

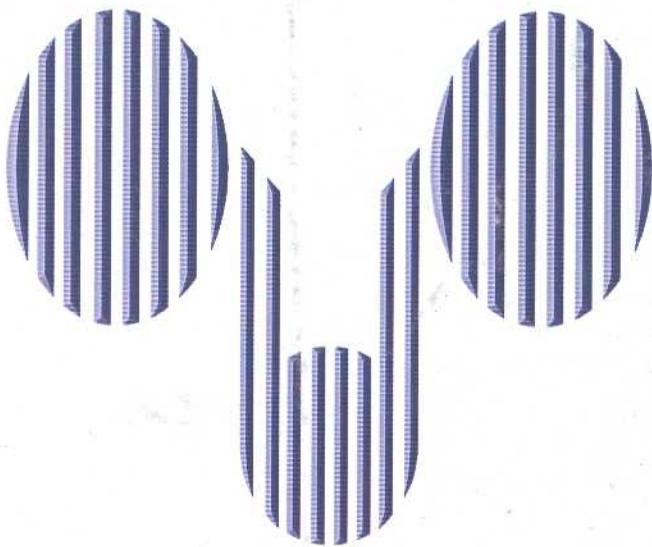
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# BRAZILIAN JOURNAL OF UROLOGY

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Volume 26, number 6

November - December, 2000

## CONTENTS

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### 556 Editor's Comment

### CLINICAL UROLOGY

---

#### 558 Renal Cryoablation Application in Nephron-Sparing Treatment

*E.F. Carvalhal, A.C. Novick, I.S. Gill*

#### 571 Ambulatory ESWL Monotherapy in Staghorn Calculi

*E.G. Silva, A. Figueiredo, C. Rabaça, J.A. Sousa, E.T. Morgado, A.P. Lopes (Editorial Comment by J. W. Segura)*

#### 579 Evaluation of Residual Stones following Percutaneous Nephrolithotomy

*M.T. Gettman, M.S. Pearle*

#### 584 Intracorporeal Holmium:YAG Laser Lithotripsy - Current Stage

*T.R. Silva, M. Maríngolo*

#### 591 Lithotripsy with Holmium:Yag Laser - Initial Results

*M.A. Fortes, L.F. Vieiravies, H.J. Vieira, A.A. Bringel, R. Araguez Jr., M.A. Corrêa*

#### 596 The Influence of Age and Prostatic Volume on Serum Prostate Specific

**Antigen Levels in Patients with Benign Prostatic Hyperplasia**

*E.A. Melo, L.A.S. Rios, D. Mattos Jr.*

#### 602 Repeated Prostate Biopsies in Men who Persist with Clinical Suspicion of Prostate Cancer

*E.P. Ribeiro, R.P. Moritz*

#### 609 Gleason Score. Comparative Study between Transrectal Prostate Biopsy and Radical Prostatectomy Specimen

*I.M. Antonopoulos, A.C.L. Pompeo, L.B. Saldanha, M.A. Arap, A. Danilovic, S. Arap*

### CASE REPORTS

---

#### 614 Bladder Herniation as Cause of Acute Urinary Obstruction

*A.E. Meller, V. Ortiz, M. Srouri*

#### 617 Posterior Urethral Valve in Adult

*U. Barroso Jr., A. Macedo Jr., M. Srouri*

#### 619 Penile Inversion after Blunt Trauma

*A.C.A. Cunha, F.P.F. Melo, R.R. Maroclo*

### PEDIATRIC UROLOGY

---

#### 621 Hypospadias. Anatomy Embryology and Reconstructive Techniques

*L.S. Baskin*

## **CONTENTS** - *continued from previous page*

---

### **INVESTIGATIVE UROLOGY** \_\_\_\_\_

- 630 Stromal Modifications in Benign Prostatic Hyperplasia as Evidenced by Glycosaminoglycan Composition**  
*L.E.M. Cardoso, W.S. Costa, F.J.B. Sampaio*

### **UROLOGICAL SURVEY** \_\_\_\_\_

- 636 Miscellaneous**

*N.R. Netto Jr.*

- 637 Imaging**

*N.M.G. Caserta*

- 639 Oncology**

*G.N. Fonseca*

- 641 Endourology and Laparoscopy**

*M.L. Lima*

### **GENERAL INFORMATION** \_\_\_\_\_

- 643 Information for Authors**

- 649 Urological Calendar**

- 651 Contents – Volume 26, 2000**

- 655 Author Index – Volume 26, 2000**

- 657 Subject Index – Volume 26, 2000**

- 660 Reviewers – Year 2000**

### **DISCLAIMER** \_\_\_\_\_

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# BRAZILIAN JOURNAL OF UROLOGY

## EDITOR'S COMMENT

The November - December 2000 issue of the Brazilian Journal of Urology presents outstanding contributions from USA, Europe, and Brazil.

Doctors Carvalhal, Novick and Gill from Cleveland Clinic, Cleveland, USA, present on page 558 both experimental and clinical results of the advanced technique of laparoscopic renal cryoablation for nephron-sparing treatment of patients with small renal tumors. The laparoscopic approach is dependent on the anatomic location of the tumor on the kidney. If the lesion is posterior or lateral, the authors employ a retroperitoneoscopic technique, while the transperitoneal route is selected if the tumors are anterior or anterolateral. The authors current practice is to offer laparoscopic renal cryoablation only to carefully selected patients who are candidates for open partial nephrectomy, having a small (< 4 cm), peripheral, exophytic, localized renal tumor located at a distance from the collecting system. In 32 patients, hospital stay was 1.8 days (22 patients were discharged within 23 hours), mean surgical time was 2.9 hours and mean blood loss was 66.8 cc (range, 10-200 cc). The authors also outlined the historical aspects, pathophysiology, radiologic evaluation, clinical experience and future horizons of this advanced technique.

Doctors Silva and co-workers from Coimbra, Portugal, present on page 571 an impressive series of 268 staghorn calculi treated by extracorporeal shock wave lithotripsy (ESWL) ambulatory monotherapy. The patients received an average of 6.1 sessions of ESWL per stone and achieved stone-free rate of 53%. All patients underwent a double-J stent placement, which lasted a whole the treatment. The most frequent complication was acute pyelonephritis (11.5%). Doctor Segura, from Mayo Clinic Rochester, Minnesota, USA, provided an important Editorial Comment which gives adequate balance on this controversial article.

Doctors Gettman and Pearle from Dallas, Texas, USA, discuss on page 579 the controversial issue of residual stones evaluation after percutaneous nephrostolithotomy (PCNL). The final recommendation is that patients with large stones requiring fragmentation at PCNL who constitute a high-risk group for residual fragments undergo non-contrast, thin-cut (5 mm) helical CT and antegrade nephrostogram on the first post-operative day to identify those patients who would benefit from second look flexible nephroscopy. Helical CT in conjunction with antegrade nephrostogram provides an accurate "road-map" with which to precisely locate residual stones at flexible nephroscopy. In those patients with residual stones, flexible nephroscopy is performed on post-operative day-two to retrieve residual fragments.

On page 621 Doctor Laurence Baskin from University of California, San Francisco, USA, one of the leaders in the study of several aspects of hypospadias, presents a comprehensive article on this subject. The author analyzed the current understanding on hypospadias etiology. Also, recent knowledge on the morphology of male and female genitalia is discussed with emphasis on surgical treatment, and the current techniques for hypospadias repair are reviewed. This article is truly relevant because the incidence of hypospadias has been increasing in Europe and USA.

## **EDITOR'S COMMENT** - *continued*

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On page 630 Doctor Cardoso and co-workers from Rio de Janeiro, Brazil, present preliminary original data on glycosaminoglycans (GAG) concentration in the prostatic tissue of patients with benign prostatic hyperplasia (BPH). The results were compared with those obtained from the transitional zone of young adults prostates. The concentration of GAG in BPH was increased by 62%. The prevailing sulfated GAG both in the normal and hyperplastic prostates is dermatan sulfate. The proportions of heparan sulfate are unchanged in both cases, whereas the content of dermatan sulfate is decreased and that of chondroitin sulfate is increased in BPH samples. The authors concluded that GAG composition in BPH differs markedly from that of the normal transitional zone. In addition, the results suggest that interstitial proteoglycans are more affected in BPH, which may result from cytokine-mediated stimulation of stromal cells.

*Dr. Francisco J.B. Sampaio*  
Editor-in-Chief

## RENAL CRYOABLATION APPLICATION IN NEPHRON-SPARING TREATMENT

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### ABSTRACT

**Purpose:** Renal cryoablation is an evolving nephron-sparing treatment alternative for select patients with small renal tumors. Initially described via either an open or percutaneous technique, renal cryoablation has been performed by a laparoscopic approach with promising results. We critically review the cumulative evidence available regarding this technique.

**Materials and Methods:** A review of the literature on both experimental and clinical studies was performed and evaluated. Historical aspects, pathophysiology, radiologic evaluation, clinical experience and future horizons of the technique are outlined.

**Results:** Two institutions have reported their clinical experience with laparoscopic renal cryoablation. Despite the lack of long-term follow-up to date, current oncologic adequacy and safety have been encouraging.

**Conclusion:** Experience with renal cryoablation is still evolving. Laparoscopic and percutaneous techniques are promising minimally invasive approaches for this developmental, nephron-sparing treatment modality. Long-term follow-up will determine the precise role of renal cryoablation in the management of selected patients with small renal tumors.

**Key words:** kidney; kidney neoplasms; cryoablation; laparoscopy; nephron-sparing  
**Braz J Urol, 26: 558-570, 2000**

### INTRODUCTION

“Renal mass” is now primarily a radiologic diagnosis. With the increasing use of abdominal ultrasonography and CT scanning, the serendipitous detection of small renal masses has increased 5-fold from 1974 to 1985 (1). This advance has contributed, in part, to a gratifying decrease in the incidence of metastatic renal cell carcinoma from 32% to 17% over the past 2 decades (2).

For the practicing urologist, the term “incidental renal mass” has progressed from being an occasional diagnostic curiosity to being a day-to-day management dilemma. The differential diagnosis of these small, solid or complex cystic, enhancing renal masses includes a variety of benign and malignant conditions. Needle biopsy remains an unreliable tool for making the histologic diagnosis of renal cell cancer, with a reported false-negative rate of 16% and a

non-diagnostic rate of 26% (3). Although small renal cell carcinomas have a slow growth rate (0.35 cm/year) (4), and are at low risk for dissemination, they nevertheless do possess the capability for systemic metastases. Accordingly, although watchful waiting has been a treatment option, current opinion has tended to favor surgical excision, especially for the younger patient. Small (< 4 cm) renal tumors can be treated efficaciously with either partial or radical nephrectomy, with comparable crude and cause-specific survival. Select patients with a localized, unilateral, small (< 4 cm) renal cell carcinoma can be successfully treated with a nephron-sparing partial nephrectomy, even when the contralateral kidney is normal (5,6).

A comprehensive review of renal cryoablation as an emergent nephron-sparing treatment alternative for small renal tumors is presented, including experimental studies and current clinical data.

Historical milestones of renal cryosurgery, the basic pathophysiology of cryotherapy and histologic and radiologic characteristics of a renal cryolesion are outlined.

## HISTORICAL ASPECTS

Cryosurgery in the treatment of cancer began in the 1850s in London when breast and cervical cancer were treated with iced saline solutions at a temperature of -18° to -22°C (7). The next advance, liquefaction of gases, occurred between 1870 to 1900. Initial investigations involved non-urologic organs like brain, liver, skin, and rectum (80). Renal cryosurgery began in the mid 1960s when Bush et al. cooled kidneys with liquid nitrogen in an effort to evaluate their functional recovery for purposes of transplantation (9). Subsequent investigations focused on the functional, morphological, histologic, radiologic, and technical (open, laparoscopic, percutaneous, puncture vs. contact) aspects

of renal cryoablation. Uchida et al. were the first to report renal cryoablation in the clinical setting. A chronology of cryosurgery of the kidney is presented in Table-1 (9-23).

## CRYOSURGICAL APPARATUS

The size and efficacy of the induced cryolesion is determined by the physical characteristics of the cryoprobe employed. Features such as nadir temperature of the cryoprobe, its thermal conductivity and surface area of renal contact directly and proportionately affect the volume and temperature of the ablated tissue. As such, a 3.4 mm probe cooling at the rate of 50°C/min to a nadir probe-tip temperature of -175°C will create a cryolesion 4 cm in diameter in 20 minutes. In contrast, an 8 mm probe cooling at the rate of 100°C/min to a nadir tip temperature of -190°C will result in a cryolesion 7 cm in diameter in 20 minutes (24). Thus, the choice of probe size depends upon the size of the tumor to be cryo-

**Table 1 – Chronology of renal cryoablation**

YEAR	AUTHOR	CONTRIBUTION
<b>Experimental Studies</b>		
1964	Bush (9)	Renal function recovery following rapid cooling with liquid nitrogen.
1974	Breining (10)	Hisotologic and autoradiographic analysis of renal cryoablation.
1979	Helpap (11)	Investigations into the cryoimmunologic response following renal cryoablation.
1981	Sindelar (12)	Ultrastructural changes following renal cryoablation.
1988	Barone (13)	Functional and morphologic effects of renal cryoinjury.
1993	Onik (14)	Ultrasound characteristics of a renal cryolesion.
1996	Stephenson (15)	Open and laparoscopic renal cryoablation in the canine model.
1996	Gill (16)	Laparoscopic and percutaneous renal cryoablation in the porcine model.
1996	Chosy (17)	Thermosensor-monitored renal cryosurgery.
1997	Nakada (18)	Puncture vs. contact renal cryoablation.
1998	Campbell (19)	Impact of renal artery clamping on cryosurgery.
<b>Clinical Studies</b>		
1995	Uchida (20)	Percutaneous renal cryoablation (2 patients)
1996	Delworth (21)	Open renal cryoablation (2 patients)
1998	Gill (22)	Laparoscopic renal cryoablation (10 patients)
1998	Rodriguez (47)	Open & laparoscopic renal cryoablation (7patients)
1999	Gill (46)	Laparoscopic renal cryoablation (32 patients)

From: Gill IS, Novick AC: Renal cryosurgery. *Urology*, 54: 215-219, 1999. Reprinted with permission.

ablated. For tumors larger than 4 cm in diameter, or those with irregular margins, multiple cryoprobes are preferable.

Various cryogens are available for use in cryosurgery. The boiling point of a particular cryogen determines the nadir temperature that the specific cryoprobe can produce. The boiling points of various cryogens at atmospheric pressure are depicted in Table-2. Two commonly used cryosurgical systems

**Table 2 – Available cryogens**

Cryogen	Boiling Point
Freon-22	-41°C
Carbon dioxide	-79°C
Nitrous dioxide	-90°C
Liquid argon	-186°C
Liquid nitrogen	-196°C

employ liquid nitrogen and liquid argon, respectively, as cryogens. In liquid nitrogen-based systems, liquid nitrogen is circulated within the cryoprobe by pressurized nitrogen gas. Liquid nitrogen boils within the cryoprobe tip, and in so doing, extracts latent heat of boiling from its immediate surrounding. For every gram of liquid nitrogen that boils and converts to gas, 209 Joules of heat are extracted. Liquid nitrogen cryoprobes are available in various diameters: 3 mm, 4.8 mm, and 8 mm, with surgical freezing zone lengths varying from 1-5 cm. Liquid argon-based systems rely on the Joule-Thompson effect, in which compressed gas or liquid under high pressure is allowed to expand rapidly through a narrow orifice into the tip cavity of the cryoprobe. Rapid cooling ensues, leading to the creation of an ice ball. The argon-based system is portable and allows for very rapid freezing rates.

## PATOPHYSIOLOGY OF THE RENAL CRYOLESION

During renal cryotherapy, the goal is to ablate the same amount of parenchyma that should be excised during an open surgical nephron-sparing procedure: the tumor itself and a surrounding margin of healthy parenchyma (8). A secondary healing process then occurs over time, with sloughing of

the devitalized tissue and replacement of that area by a fibrotic scar. It is clear that certain aspects of cryosurgery are essential, including a rapid freezing, slow thawing, and a repetition of the freeze-thaw cycle (24).

Rapid intracellular ice formation causes irreversible cell death. Tissue interstitium is incorporated by the freezing process in a sequential manner: extracellular matrix freezes initially followed by intracellular freezing. The latter is thought to be the terminal, lethal event. The mechanism underlying tissue cryoinjury is thought to involve a)- immediate cellular damage and, b)- delayed microcirculatory failure. Mazur proposed a two-step theory for cellular damage: ice formation occurs initially in the extracellular space, causing the extracellular fluid to become hyperosmotic (25). Because the cell membrane may be a barrier to the freezing process, the intracellular fluid, although supercooled, remains unfrozen at this stage. To equilibrate chemical osmolality, water permeates out from the cell along the osmotic gradient into the extracellular compartment. This in turn increases the osmolality of the intracellular fluid, resulting in solute concentration and intracellular dehydration. As extracellular ice crystals grow, cells shrink further, sustaining desiccation injury to intracellular structures. This comprises the first step of cellular chemical injury (26). Continued rapid supercooling leads to the second step of cellular damage. Cell membrane dysfunction occurs at temperatures below -10°C, leading to the critical event: intracellular ice formation. Intracellular ice irreversibly disrupts cell organelles and the cell membrane, which is lethal. During thawing, the extracellular compartment becomes briefly hypotonic. Water re-enters the cell causing cell swelling, and possibly cell membrane rupture.

Delayed microcirculatory failure manifests during the thaw phase of the freeze-thaw cycle, leading to circulation arrest and cellular anoxia. Tissue cooling sequentially leads to vasoconstriction, decrease in blood flow, and ultimately, cessation of blood flow. During the 10-20 minute initial thawing period, circulation is restored to the cryoablated area. Experimental hepatic cryoablation has demonstrated the formation of continuous ice crystals along the lumen

of the small blood vessels leading to dilation and destruction of the structural integrity of the microvasculature. Progressive failure of the microcirculation occurs due to a cascade of events: endothelial layer destruction causing vessel walls to become porous, interstitial edema, platelet aggregation, microthrombii, and ultimately vascular congestion and obliteration (24). Although small blood vessel lumens are destroyed within 4 hours after thawing, larger arterioles may remain patent for periods of up to 24 hours (27). Cells that survive freezing's initial assault are destroyed by this secondary impact of ischemia (28). Repetition of the rapid freeze-slow thaw cycle potentiates this damage. The cryoablated area is thus rendered ischemic, leading ultimately to a circumscribed necrosis.

The dimensions of a cryolesion depend upon multiple factors. As already mentioned, the colder the nadir temperature of the cryoprobe tip, the larger the cryolesion. The duration of freezing, the actual area of contact between the cryoprobe and the targeted tissue, and the rate of cooling are important variables. Cell destruction is dramatically enhanced by increasing the cooling rate from 5° C/min to 25° C/min. Tissue vascularity is an important factor, and in general, the more vascular the targeted tissue, the slower is the rate of cryoablation. This phenomenon is termed the "heat sink" effect (29). Flow of warm blood through large adjacent vessels may dissipate the cold temperature of the evolving cryolesion, thereby slowing its rate of growth. Theoretically, this may decrease the efficiency of cryoablation and lead to asymmetric ice ball formation. The "heat sink" effect can, on occasion, be used to therapeutic advantage. To wit, a urethral warming device is employed during prostate cryoablation, in order to protect the urethra from cryodamage. Other biologic characteristics like specific heat, density, and thermal conductivity of the particular tissue or organ also impact on the efficacy with which it undergoes cryodestruction.

Lethal temperature for achieving reliable cell death is approximately -40°C. For normal and cancerous renal cells, a temperature of -20°C causes uniform necrosis. In an elegant study, Chosy, Nakada et al. showed that complete necrosis of in-vivo porcine renal parenchyma occurred uniformly at temperatures

of -19.4°C or lower in all instances (13 of 13 tissue samples). However, when the temperature ranged between -19.4°C and 0°C, tissue necrosis was present in only 80% of renal samples (17).

The temperature within a given cryolesion is not uniform, increasing exponentially as a function of the distance from the cryoprobe. Thus, the temperature at the periphery of the ice-ball is significantly higher than the core temperature at its center (30,31). Accordingly, the visible outer edge of the ice-ball is usually at 0°C, although the temperature at its center (cryoprobe tip temperature) may be -196°C. The temperature begins to decrease incrementally from the periphery towards the center of the ice-ball: it is -20°C at a distance of 4 mm, and -40°C at a distance of 6 mm inside the periphery. In this regard, valuable data were provided by two recent experimental studies wherein a 3.4 mm cryoprobe was used to create renal cryolesions with a diameter of 3.2 cm. Campbell et al. confirmed that the target temperature of -20°C was achieved at a distance of 3.1 mm inside the edge of the ice-ball in all 10 canine kidneys (19). In Chosy's study, all 17 tissue samples taken from within a 3.2-cm diameter area ("within 16 mm of the probe insertion site") were uniformly ablated. However, the directly visible extent of the ice-ball was not an absolute predictor of cellular necrosis: 2 of 18 (11%) of samples obtained from within the area encompassed by the visible ice-ball contained viable tissue. The authors speculated that sampling error as well as the ellipsoid shape of the advancing ice-ball may have contributed to these results (17). Thus, to ensure complete cell kill, the ice-ball must extend well beyond the margins of the targeted tumor. Based on these data and our own laboratory observations, we routinely attempt to extend the ice-ball at least one 1 cm beyond the edge of the tumor, as determined both by laparoscopic visualization and real-time ultrasonographic imaging. This margin should be sufficient to achieve the desired lethal temperature of -40°C within the entire extent of the tumor.

It appears evident that a double freeze-thaw cycle is a primary prerequisite for reliable cryo-induced cell death (24,32). A comparison of single and double freeze-thaw cycles has not been performed as regards the kidney. For prostate adenocarcinoma,

Tatsutani and co-workers showed that the percentage of cells destroyed by freezing to -20°C (cooling rate 25°C/min.) was approximately 80% by the single freeze-thaw cycle compared with 100% by the double freeze-thaw cycle at the same temperature (33). Shinohara and colleagues found that prostate cryoablation induced undetectable PSA levels in 35% of patients following a single freeze-thaw cycle compared with 80% following a double freeze-thaw cycle (34).

## HISTOLOGY

Histologically, the cryoablated tissue reveals progressive changes over time, from typical findings of cell death and tissue non-viability to chronic signs of inflammation, fibrosis and scarring. Initially (1 hour), the renal cryolesion macroscopically demonstrates areas of dark red discoloration consistent with interstitial hemorrhage with an abrupt line of demarcation from the surrounding healthy renal parenchyma. Microscopically, generalized vascular congestion is evident, with only subtle signs of early coagulation necrosis. Hemorrhagic glomeruli, fibrin deposition within capillaries and near complete exfoliation of the urothelium covering the cryoablated papillae is evident (35). The inflammatory response is minimal with only a mild infiltration of polymorphonuclear neutrophils (10). Marked ultrastructural evidence of irreversible cell death is also shown on electron microscopy, such as partial fragmentation and cytoplasmic vacuolization of membranes, disruption of outer membranes and internal crystal of mitochondria, chromatin condensation and loss of nuclear membrane, hemorrhage into glomerular spaces and disruption of epithelial podocytes of glomeruli (12).

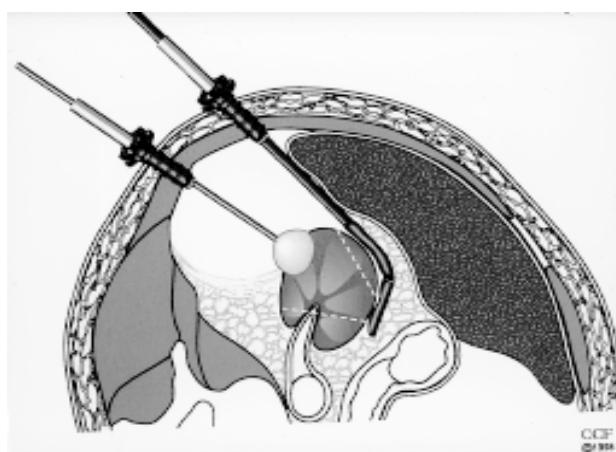
A sharply demarcated, deep-red cryolesion is readily apparent macroscopically after 24 hours. On microscopic examination, complete coagulation necrosis is evident centrally, surrounded by a 0.3 mm-8 mm transitional zone of partial necrosis, which abuts normal renal parenchyma. Loss of cell borders, absence of cytoplasmic organelles, and ghost renal tubules are easily identified in the area of complete necrosis. Hyalinization of glomerular and tubular cellular structure is seen, while nuclear py-

knosis is evident universally in the glomerulii and blood vessels. When examined under electron microscopy, tubular cells appear as proteinaceous aggregates, completely devoid of membranes, while glomerulii are degenerated and glomerular spaces are filled with necrotic cellular debris. Capillary basement membranes remain intact with large intravascular thrombi (12). The zone of partial necrosis contains some viable cells, thus representing an area of sublethal injury. Glomerular architecture is lost and proteinaceous casts are visible in the collecting tubules. Considerable infiltration of polymorphonuclear leucocytes is seen.

Fibrotic changes and a typical contracted scar are eventually seen after 1 month following renal cryoablation, when chronic inflammation, fibrotic glomerulii and tubules, and no evidence of viable renal parenchyma are observed under microscopic examination.

## RADIOLOGIC EVALUATION

The advances in diagnostic and intraoperative imaging techniques are directly related to the development of cryosurgery. The ultrasound characteristics of a renal cryolesion were initially reported



**Figure 1 – Renal cryoablation under direct intraoperative ultrasound and laparoscopic control. The ice ball must extend 1 cm beyond the margins of the tumor. The ultrasound probe is placed in direct contact with the kidney directly opposite to the tumor. From: Gill IS, Novick AC, Soble JJ: Laparoscopic renal cryoablation: initial clinical series. Urology, 52: 543-551, 1998 (Reprinted with permission).**



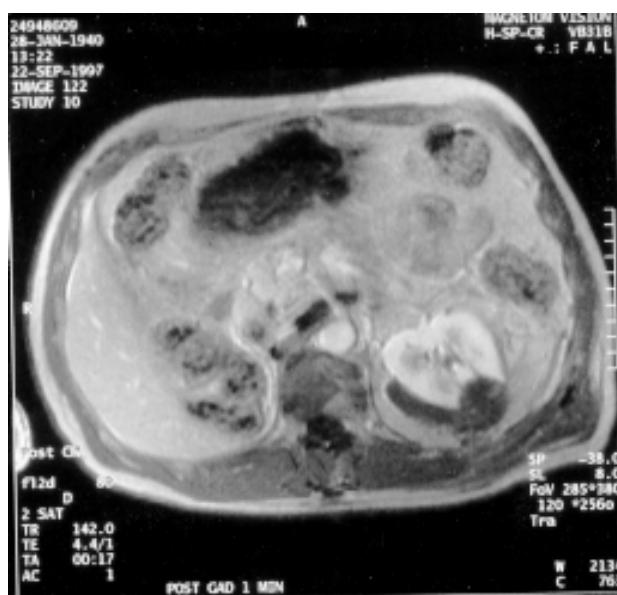
**Figure 2 – Ultrasound monitoring of the evolving cryolesion.** Note: 1)- The crescent hyperechoic leading edge and the anechoic body of the iceball under ultrasound control, and 2)- Picture-in-picture laparoscopic view of the iceball.

by Onik et al. in the porcine model, which include an advancing hyperechoic edge with posterior acoustic shadowing (14). As such, intraoperative ultrasonography has been the imaging modality employed by virtually all reported studies of renal cryoablation to date. In our clinical laparoscopic renal cryoablation experience, we position a flexible, steerable, endoscopic, color-Doppler ultrasound probe within Gerota's fascia, in direct contact with the renal surface (Figure-1) for intraoperative monitoring (Panther 2002, Y-Ducer model 8555, Gentofte, Germany) (22). Tumor size, echogenicity, vascularity and distance from the renal sinus are measured. The remainder of the kidney is scanned for any satellite nodules. Ultrasonography is employed to guide the needle biopsy, and the subsequent cryoprobe placement into the center of the tumor such that the probe tip is positioned at, or just beyond, the deep margin of the tumor. The evolving cryolesion is then sonographically monitored real-time until complete ablation of the tumor is confirmed and the ice ball is noted to extend 1 cm beyond the tumor margins circumferentially. Distance of the edge of the cryolesion from the renal sinus is measured, thus minimizing chances of inadvertent cryoinjury to the collecting system (22).

The intraoperative laparoscopic ultrasound characteristics of the renal tumors are heterogeneous echogenicity or mild hyperechogenicity, which con-

trasts with the hyperechoic renal sinus fat. Combined with direct laparoscopic visualization, real-time laparoscopic ultrasound is essential for precise positioning of the cryoprobe tip up to the deep margin of the tumor. Adequate localization of the leading edge of the ice ball as it obliterates the tumor margin, as well as the typical aspect of an enlarging, hyperechoic rim with posterior echo loss of the cryolesion, is easily obtained (Figure-2). Mean tumor size on intraoperative ultrasound (2 cm) was 14% smaller than the mean tumor size on preoperative CT scanning (2.4 cm). This 14% size differential, which for a 2.5-cm renal mass would represent only 3-4 mm, is probably attributable to the angle in which ultrasound measurements were obtained (36).

We selected magnetic resonance imaging as our preferred modality for postoperative follow-up of renal cryolesions, due to its superior soft tissue contrast resolution and multiplanar imaging capability. Successful renal cryoablation is visualized as non-enhancement of the lesion following gadolinium administration (Figure-3). We routinely perform MRI, with and without gadolinium enhancement, on days 1, 30, 60, and 90 postoperatively, in order to assess the kidney and surrounding structures. All cryolesions



**Figure 3 – Successful renal cryoablation is visualized as non-enhancement of the lesion following gadolinium administration, as seen on day 1 MRI.**

were isointense to the adjacent normal renal parenchyma on  $T_1$  weighted images and hypointense on  $T_2$  weighted images. A hyperintense peripheral rim at the border between the cryolesion and the kidney on day 1 MRI scans  $T_1$  weighted images was observed in some cases. After 30 days, an increase in signal intensity on both  $T_1$  and  $T_2$  weighted images was constantly detected, but no gadolinium enhancement of the cryolesion occurred. Radiologist familiarity with these sequential MRI findings allows accurate assessment of spontaneous contraction of the cryolesion over time. We reported a decrease in MRI size of the cryolesion by 14%, 23%, and 40% at 1, 2, and 3 months postoperatively in our 10 initial patients (22). In fact, of the 7 patients who have completed now a 1 year follow-up MRI scan, the cryoablated renal tumor is no longer detected in 3. The other 4 patients observed a decrease in size by 57%.

## **RENAL CRYOABLATION: EXPERIMENTAL DATA**

Many questions needed to be addressed experimentally before embarking on clinical renal cryosurgery. The following experimental data provides the background for the reported clinical experience.

### **What is the Natural History of a Renal Cryolesion?**

The size of a renal cryolesion contracts over time (17). While on postoperative day 8 a large central area of coagulative necrosis surrounded by a narrow zone of sublethal injury is observed, at 3 months, the area of necrosis is completely absorbed and replaced by fibrosis. In a porcine study involving healthy kidneys, we noted a macroscopic decrease in size of the renal cryolesion by 42% at day 7, 52% at day 30, and complete resorption of the lesion by day 90 (16).

### **What Happens if the Ice-ball comes in Contact with Adjacent Structures?**

Inadvertent contact of the ice ball or the active cryoprobe with adjacent structures is capable of producing disastrous consequences. Contact of the cryolesion with a loop of small bowel during porcine

laparoscopic renal cryoablation led to complete small bowel obstruction in one animal in our study (16). Also, a significant stricture of the ureteropelvic junction following open renal cryoablation in the canine model has been reported. These reports point to the need of precisely monitoring the intraoperative cryoprobe positioning and cryolesion development. Concern about cryoinjury to the ureter led the authors to recommend adequate mobilization of the kidney away from the ureter prior to cryoablation of the lower renal pole (19).

### **Is Renal Artery Clamping a Helpful Adjunct During Cryoablation?**

Since constant perfusion of an organ with warm blood could theoretically serve to dissipate the cold temperature during cryosurgery, the effects of renal arterial occlusion on the freezing process were studied. Campbell et al. demonstrated that, based on a canine model of renal cryoablation, renal arterial occlusion during clinical cryoablation was of no practical advantage (19). Occlusion of the main renal artery (5 animals) did not result in increased rate of cooling or differences in the nadir temperature achieved when compared to a control group (5 animals without arterial clamping). The target temperature of -20°C was achieved 1.8 mm inside the edge of the ice-ball in the group with arterial occlusion, and 2.0 mm inside the edge of the ice ball in the group without arterial occlusion. Also, no significant differences were found in terms of mean diameter of the infarcted zone between the 2 groups.

### **How Accurate is Ultrasonography in Evaluating the Size of the Renal Cryolesion?**

Stephenson et al. created surface contact renal cryolesions in 12 dogs (15). Ultrasound measurements for depth and diameter were determined for each cryolesion. Upon thawing, direct tissue measurements of the easily discernible cryolesion were obtained. The ultrasonic and direct physical measurements were closely concordant for both depth and width, with a correlation coefficient of  $r = 0.9295$  ( $p = 0.0001$ ). In patients undergoing radical nephrectomy, Orihueta et al. performed in vivo cryotherapy of the renal cell cancer just before removal of the

kidney (37). A 3-mm cryoprobe (tip temperature -180°C) was employed under ultrasound control. Final tissue temperature at 7.5 mm, 15 mm, and 22.5 mm away from the cryoprobe was noted to be -90°C, -90°C, and -20°C, respectively. Histology showed well demarcated, complete necrosis, resembling hemorrhagic infarct up to 18 mm away from the cryoprobe. The authors found good correlation between ultrasound imaging and the physical dimensions of the cryolesion. Long & Faller described a porcine model of ultrasound-guided percutaneous cryoablation of the kidney (38). They demonstrated the feasibility of the technique regarding tolerability and focal destruction of target areas. However, the consistent difficulty in adequately monitoring the actual intraoperative size of the ice ball with a real-time 2-dimensional ultrasound, due to anatomic interference by the spine and lower ribcage, was a significant limitation of the percutaneous technique employed.

### **What is the Impact of Renal Cryoablation on Overall Kidney Function?**

Functional impact is determined by the amount of renal parenchyma ablated by the ice-ball. The selective destruction of target areas under precise intraoperative monitoring has been essential to preserve normal renal parenchyma. In a solitary kidney canine model (baseline serum creatinine 0.6-0.9 mg/dL), creation of a cryolesion (mean diameter 3.2 cm) resulted in a transient elevation of serum creatinine on postoperative day 2 (1.0-1.9 mg/dL), and a final serum creatinine of 1.0-1.5 mg/dL by day 28 (19). When renal cryoablation was performed bilaterally in the porcine model, mean serum creatinine levels at day 0, 1, 3, and 7 were 1.5, 2.3, 1.8, and 1.4 mg/dL, respectively (16).

### **How do Temperature and Distance from the Cryoprobe Impact upon the Degree of Renal Parenchymal Destruction and Collecting System Damage?**

The ability of tissue destruction and complete necrosis depends directly upon the nadir temperature achieved at that location. Chosy et al. demonstrated that a temperature of -19.4°C or lower is necessary for promoting complete tissue necrosis (17). The tem-

perature at the edge of the ice ball is approximately 0°C, and a temperature of -20°C is routinely achieved 3.1 mm inside the ultrasonographically visualized edge of the ice ball with complete tissue necrosis on histology. Therefore, circumferential extension of the ice ball for at least 3.1-mm beyond the tumor margin ensures adequate intralesional cooling (19).

Regarding the effect of the cryoinjury to the renal collecting system, an experimental study addressing this question has been recently presented by Sung et al. (39). In a porcine model, 18 kidneys were submitted *in vivo* to intentional cryoinjury to the pelviocaliceal system under ultrasound and retrograde ureteropyelogram control, and the acute and long-term (3 months) sequelae were analyzed. After 1 month, regrowth of normal urothelium was noted, with minimal scarring of the lamina propria and smooth muscle, while the adjacent parenchyma was replaced by fibrous scar. Ex-vivo retrograde pyelogram revealed watertight healing of the caliceal system when no physical cryoprobe puncture injury to the renal pelvis was documented.

### **Does Renal Cryoablation Lead to Systemic Hypothermia?**

Renal cryoablation does not alter renal vein or renal arterial temperatures. Perlmutter et al. created renal cryolesions with a probe tip temperature of -147.7°C. Baseline renal artery and renal vein temperatures were 35.3°C and 34.9°C, respectively. Following cryoablation, mean renal artery and vein temperatures were 35.4°C and 34.5°C, respectively (38,40). In our study, systemic (esophageal) temperature during renal cryoablation in a porcine model was noted to decrease only by 1°F to 3°F (16).

## **RENAL CRYOABLATION: CLINICAL STUDIES**

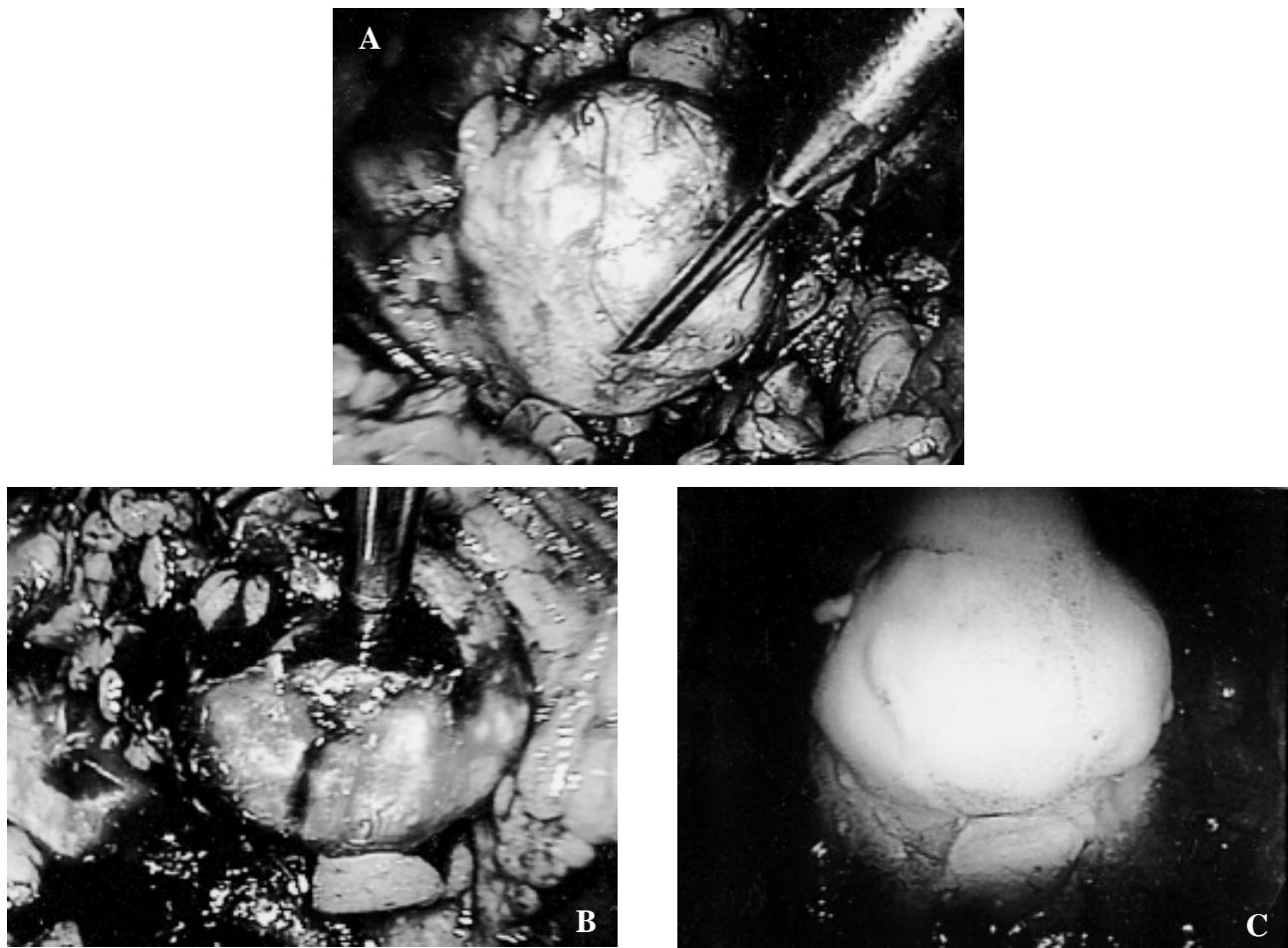
The first reported clinical study of cryoablation as a nephron-sparing procedure was published by Delworth et al., who performed open cryoablation in 2 patients with a solitary kidney (21). The first patient had a 3 cm renal cell cancer and the second had a 10 cm angiomyolipoma. Operative time was 3.5 hours and 4.5 hours, with a blood loss of 200

cc and 700 cc, respectively. Postoperative serum creatinine was 1.3 mg% in both patients and follow-up consisted of a MRI at one month, revealing a significant decrease of the renal carcinoma dimensions and at 3 months, showing a 10% enlargement in size of the angiomyolipoma. Although no pathologic data were included in the study, the authors concluded that renal cryotherapy could be performed safely with minimal loss of renal function.

Two patients with symptomatic, metastatic renal cell carcinoma were treated with percutaneous renal cryoablation by Uchida et al. in 1995 (20). A percutaneous puncture was performed under ultrasound control into the center of the tumor, and tract dilation to 24F was achieved for cryoprobe insertion. Although follow-up was short in these patients and

no pathologic data was available, as they died of metastatic disease at 1 and 10 months postoperatively, follow-up CT scans showed shrinkage of the cryolesion by 20% at 1 month in one patient, and by 81% at 8 months in the second patient (20).

Recently, Shingleton et al. presented their clinical experience of 17 patients treated with percutaneous cryoablation utilizing an interventional MRI unit, under general or local anesthesia with intravenous sedation (41). Patients were discharged home the following day and no complications were reported. Although the authors did not perform control biopsies after the procedure, 94% of tumors were found to have no enhancement on short-term follow-up MRI/CT scan (1-6 mo). Similarly, initial results with other energy sources like the laser or radiofrequency inter-



**Figure 4 – Steps of laparoscopic renal cryoablation: A)- Dissection of the peripheral renal lesion; B)- Puncture of the renal lesion with the cryoprobe, under direct laparoscopic and ultrasound monitoring and C)- Laparoscopic view of the renal cryolesion.**

stitial thermoablation under MRI guidance have been reported percutaneously (42-45) and need to be further evaluated.

In our opinion, percutaneous cryoablation may become a potential outpatient nephron-sparing alternative modality in the future. However, the percutaneous approach must not be applied to anterior parenchymal lesions due to the risk of injury to intra-abdominal organs, which limits its applicability to only posteriorly located tumors.

Two centers have provided clinical data on laparoscopic renal cryoablation to date (46,47). We first reported the initial series of 10 patients in the literature in 1998 (22), and have now expanded our experience to 50 carefully selected patients. Our laparoscopic approach is dependent on the anatomic location of the tumor on the kidney. If the lesion is posterior or lateral, we employ a retroperitoneoscopic technique, while the transperitoneal route is selected if the tumors are anterior or anterolateral. During retroperitoneoscopic cryosurgery, a 3-port approach in full flank position is preferred, while a 4-port approach with the patient in a 45-degree oblique position is developed for the transperitoneal procedure. Our technique during laparoscopic renal cryoablation includes complete mobilization of the kidney within Gerota's fascia, excision of the perirenal fat overlying the tumor for histopathologic evaluation, intraoperative imaging of the tumor and remainder of the kidney with a laparoscopic, color-Doppler ultrasound probe, needle biopsy of the tumor and puncture cryoablation (with 4.8 mm cryoprobe) (Figure-4). As postoperative hemorrhage is a concern, careful confirmation of hemostasis after the procedure is undertaken, with observation under reduced CO<sub>2</sub> pressure. If necessary, hemostatic compression with a piece of Surgicel or the use of the argon beam coagulator after gentle relieve of the cryoprobe. Our current practice is to offer laparoscopic renal cryoablation only to carefully selected patients who are candidates for open partial nephrectomy at our center, having a small (< 4 cm), peripheral, exophytic, localized renal tumor located at a distance from the collecting system. In the initial 10 patients (mean age 67.6 years), mean blood loss was 75 cc, cryoablation time was 12.9 minutes and total surgical time was 2.4 hours. Hospi-

tal stay was < 23 hours in 9 of 10 patients. One patient, who was on chronic Coumadin therapy preoperatively, developed an asymptomatic perirenal hematoma due to trauma from a laparoscopic fan retractor, which was treated conservatively. In 32 patients, hospital stay was 1.8 days (22 patients were discharged within 23 hours), mean surgical time was 2.9 hours and mean blood loss was 66.8 cc (range, 10-200 cc) (48). In our expanded experience with 50 patients, no patient required open conversion. By now, 22 patients have undergone a 6-month follow-up CT-directed biopsy of the cryoablated site, with negative results. One patient with previously ablated renal cancer and a negative 6-month CT-directed biopsy was re-biopsied at 9 months for a suspicious nodule on a subsequent follow-up MRI scan. Renal cell carcinoma was demonstrated at biopsy, and laparoscopic radical nephrectomy was performed (49). Twenty-four patients treated by our group were evaluated regarding the impact of cryoablation on renal function and blood pressure for a minimum of 6 months after treatment. No deleterious effect on serum creatinine or blood pressure over a mean follow-up of 20 months was detected, including 5 patients with a solitary kidney (unpublished data).

Rodriguez et al. recently presented their experience with 9 patients with exophytic renal masses with a mean size of 2 cm (23). Mean blood loss was 140 cc and hospital stay was 3 days. There were no intraoperative complications and, at a mean follow-up of 5 months, no tumor recurrences were noted as evaluated by follow-up CT scans.

To date, there has been no report in the literature of urinary fistula or cryoinjury to the bowel, ureter or surrounding structures following clinical laparoscopic renal cryoablation (22,23,46,47,50). However, due to the reported experimental evidence regarding adjacent tissue cryoinjury from inadvertent physical contact of the ice ball, extreme care must be taken to maintain the iceball under complete laparoscopic visualization at all times.

## FUTURE HORIZONS

Experience with laparoscopic renal cryoablation is still evolving. Nevertheless, cumulative data

regarding its safety and efficacy has been presented. Comparatively to the prostate, the kidney is an ideal solid organ for cryoablation. It usually harbors unifocal malignancy and can be easily mobilized laparoscopically, enabling a higher degree of precision in completely involving the targeted area. Long-term oncologic adequacy still needs to be documented before its widespread use recommendation, although recent results are promising. Clinical and radiologic follow-up of these patients will be critical for determining local recurrence and the cancer-specific survival rate following renal cryoablation. Although experimental data suggest adequate healing of the cryodamaged pelviocaliceal system, central tumors still constitute a contraindication for cryoablation. In the other hand, treatment of selected posteriorly located tumors by entirely percutaneous techniques is already possible. Further development of three-dimensional ultrasound and MRI-compatible cryoprobes may allow improved imaging of the acute and chronic renal cryolesion, establishing another minimally invasive alternative for selected cases in an outpatient basis.

Research directed towards the periphery of the cryolesion, the so-called sublethal zone of destruction, is a promising avenue for future investigation. This outer 2-4 cm rim of the cryolesion is the area where some cancer cells may potentially survive lethal injury. Cryoablation causes cells to die by either apoptosis or necrosis. It has been shown that the apoptosis-inhibitor IDN-1529 protects prostate cancer cells (PC-3 cell line) from death even when exposed to temperatures ranging from -10°C to -75°C (51). As a corollary, it is plausible that apoptotic-activators may actually promote the death of certain freeze-tolerant cancer cells, such as those located in the peripheral, sublethal zone of a cryolesion. Indeed, Clarke et al. have already shown that canine kidney cell cultures (MDCK) treated with 5-Fluorouracil 2 days prior to freezing lost all cell viability and failed to recover. This degree of cell damage was significantly greater than the loss of cell viability induced by either freezing alone or 5-Fluorouracil alone (52). Such cryosurgical modeling takes advantage of the possible apoptosis-inducing synergistic effects of combination treatments such as radiation and chemo-

therapy regimens already employed in the treatment of certain cancers. Optimal use of such cryoadjuncts may further enhance the lethal effects of cryosurgery.

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## AMBULATORY ESWL MONOTHERAPY IN STAGHORN CALCULI

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### ABSTRACT

**Objective:** To evaluate the efficacy of ambulatory extracorporeal shock wave lithotripsy monotherapy in the treatment of staghorn calculi.

**Materials and Methods:** Using piezoelectric lithotriptors (EDAP-LT01 or LT02), 268 staghorn calculi were treated. One hundred and forty three were complete and 125 were partial (65 filled the renal pelvis + one calyceal system, and 60 filled the renal pelvis + two calyceal systems).

**Results:** Eight patients abandoned the treatment, giving 260 available cases.

The overall stone free rate on ultrasound control was 53% (62% when controlled by x-ray), after an average of 6.1 sessions/stone. Cure rate was 92%, when including kidneys with clinically insignificant residual fragments (smaller than 2 mm occupying an area < 10 mm<sup>2</sup>). Acute pyelonephritis was a frequent complication (11.5%), most often in association with dislodgment of the ureteral stent catheter. Loss of renal function occurred in one case.

**Conclusion:** The authors conclude that this treatment offers important advantages over open surgery or percutaneous nephrolithotomy, which should not be underestimated.

**Key words:** kidney; calculi; urolithiasis; lithotripsy; ESWL; staghorn calculi

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### INTRODUCTION

When Extracorporeal Shock Wave Lithotripsy (ESWL) was first introduced in clinical practice in 1980, staghorn calculi, infected stones and hydronephrotic kidneys were considered not eligible for this modality of treatment. Within these last two decades, selection criteria for the treatment of urolithiasis have changed. Now, most centers accept ESWL as the first choice treatment for urinary stones, including staghorn calculi, either as monotherapy or in association with Percutaneous Nephrolithotomy (PNL). From the beginning of our experience, in 1987, we have used Ambulatory Extracorporeal Shock Wave Lithotripsy Monotherapy (AESWLM) in most cases of urinary stones. The results of our experience in 268 staghorn calculi are herein presented.

### MATERIALS AND METHODS

Between October 1987 and December 1998, 8,100 ESWL sessions were performed for the treatment of 4,020 stones, using an EDAP LT01 and LT02 lithotriptors (both working simultaneously since 1997).

Two hundred and fifty seven patients had staghorn calculi, 11 of them bilaterally, for a total of 268 staghorn calculi treated. The average age of the patients with staghorn calculi was 44 years (4-77) and the female to male ratio was 2.95/1.

One hundred and forty two staghorn calculi were complete (Rocco 5), and 126 were partial (Rocco 4), 65 filling the renal pelvis plus one calyceal system, and 60 filling the renal pelvis plus 2 calyceal systems (1). The stone size varied between 20 x 25 mm to 141 x 82 mm and the area varied between 490 mm<sup>2</sup> to 2,700 mm<sup>2</sup>, for an average of 1,050 mm<sup>2</sup>.

Pyelocalyceal morphology was normal in 161 patients. Moderate hydronephrosis was present in 24 cases (14 complete and 10 partial calculi), one or more calyceal dilatations were present in 64 cases (37 complete and 27 partial calculi), in nine cases there was a giant hydronephrosis with marked impairment of renal function and 10 cases revealed evident signs of chronic pyelonephritis.

Seventy two patients had persistent urinary tract infections (UTI) and 10 patients had a solitary kidney. The ureteric and pyelocalcial morphology was analyzed in all patients by a previous intravenous pyelography (IVP). A double-J stent catheter was introduced before treatment in all but the first 17 cases. In all patients prophylactic antibiotics were administered, even in the cases with non infected stones. Treatment sessions were performed without anesthesia. With rare exception, almost all of the patients were administered analgesics or ansiolytics. Patients were put in dorsal or lateral decubitus, according to the stone portion chosen to be destroyed in the session (2). Taking advantage of the lithotriptor's small focus and its corrosive effect, several selective disintegrations were performed in each session. The mean frequency used was 3.8 c/s at 85-100% of power, and each treatment session lasted, on average, 58 minutes (20-70 min). All patients returned home after each treatment, going back to work the next day. Patients were told to adopt a position that would make the elimination of the fragments easier (3). The interval between the sessions was never less than 2 weeks. In cases with infectious stones and hydronephrotic kidneys or volumi-

nous hydrocalyces the intervals were even longer. The double-J stent was changed whenever an obstructive pyelonephritis developed, when the patient complained of bladder symptoms or every three months. Ultrasonography and a final IVP were used to assess treatment results. The evolution of the treatment and its results, as well as the decision to suspend or continue it was made by the urologists of the ESWL Unity.

## RESULTS

All treatment sessions were well tolerated by the patients. Eight patients were lost to follow-up, and were excluded in the results. Classic surgery was performed in seven cases, since no fragments were eliminated after six sessions of ESWL. The number of sessions per case varied between 2 to 18 (average 6.1-8 in complete staghorn calculi, 4.3 in partial staghorn calculi with two calyceal groups involved, and 4.2 in the remaining partial staghorn calculi). The average duration of the treatment was 4.6 months (2-39 weeks per stone).

Complete destruction of the calculi without residual fragments was achieved in 161 (62%) of the 260 cases, when x-ray control was used. This result dropped to 138 (53%) when ecographic control was used (Table).

The success rate rises to 92%, if kidneys with clinically insignificant residual fragments (< 2 mm occupying an area < 10 mm<sup>2</sup>) are included. There were no clinically significant differences between treatment results for the cases with complete vs. partial stag-

**Table - Final results for complete vs. partial staghorn calculi. The seven cases that shown no destruction are included in the group of residual stones > 2 mm.**

<b>Final Results</b>	<b>Without Residual Stones</b>		<b>Residual Stones &lt; 2mm &lt; 10mm<sup>2</sup></b>		<b>Residual Stones &gt; 2 mm &gt; 10 mm<sup>2</sup></b>	
	<b>Rx Control</b>	<b>Ecographic Control</b>	<b>Rx Control</b>	<b>Ecographic Control</b>	<b>Rx Control</b>	
Complete n = 134	76	63	41	54		17
Partial n = 126	85	75	37	47		4
Total n = 260	161	138	78	101		21
	(62%)	(53%)	(30%)	(38.8%)		(8%)

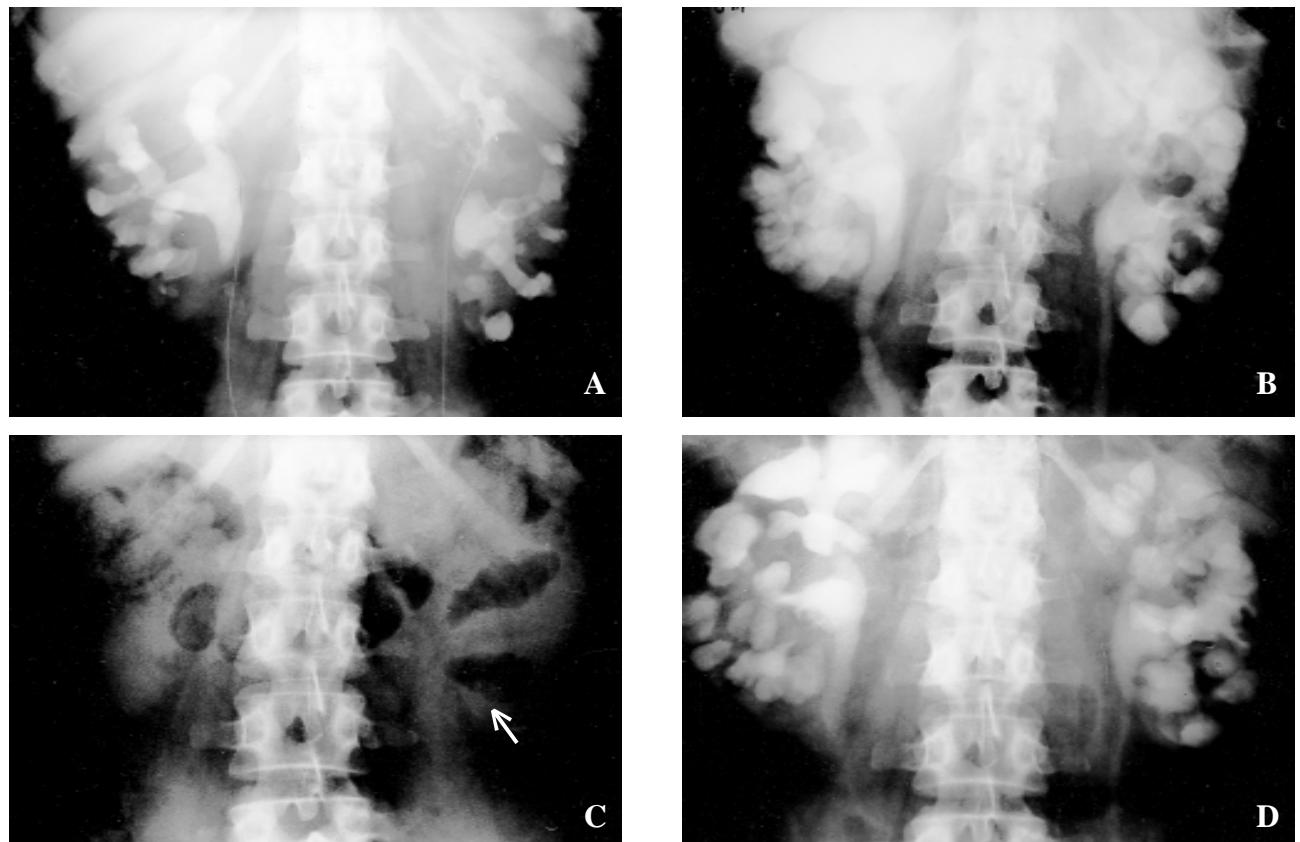
horn calculi (Table). Among the nine patients with reduced renal function (and marked hydronephrosis), four became free of stones, two have residual fragments < 2 mm, and three have residual fragments > 2 mm < 10 mm. Thirty two (44.4%) of the 72 patients with persistent UTI became free of infection, 23 (31.9%) have infrequent episodes of UTI easily controlled by antibiotics, and 17 (23.6%) still need permanent antibiotic treatment. In 16 patients, a different bacterial species was detected.

The overall rate of severe complications was small. Three patients developed severe pyelonephritis (pain and temperature over 38°C) associated with partial spontaneous dislodgment of the double-J stent catheter. Percutaneous nephrostomy was done in 2, both presenting marked hydronephrosis. The third patient lost his kidney as consequence of staying at home with fever for 2 weeks before returning to our center. Moderate pyelonephritis (temperature below 38°C) occurred in 30 cases (11.5%) during the first three days after treatment, despite being under antibiotic therapy. Ten of these patients had a normal pyelocalyceal morphology (6 partial and 4 complete staghorn calculi), 20 had one or more calyceal dilatation (8 complete and 4 partial), and 8 had moderate hydronephrosis (5 complete and 3 partial). As a consequence of acute pyelonephritis, one kidney function was lost, severe functional impairment occurred in another, and moderate decrease was observed in four kidneys, all of them with infectious stones. Thirty cases of persistent "steinstrasse" (11.5%), 18 occurring in cases of complete and 12 in cases of partial staghorn calculi, were successfully treated either by ureteroscopic ultrasonic or ballistic lithotripsy (20 cases with 4 nephrostomies) or by "in situ" ESWL (10 cases). A case where a voluminous fragment became impacted in the middle third of the ureter needed open surgery, after an ureteroscopic failure. Massive calcification of the bladder end of the double J stent occurred in nine patients (3.5%), and was successfully treated by ESWL. The mean duration of hospitalization for patients requiring auxiliary procedures was three days. One hundred and twelve patients remain under our control. Sixty eight needed from 1 to 3 short sessions of ESWL over small recurrent calyceal calculi.

## DISCUSSION

We have adopted the policy of trying ESWL in most cases of urolithiasis since we started using this treatment modality in 1987. Our experience shows good results in the treatment of staghorn calculi, with complete clearance of the stones in 53% of the cases, and clinically insignificant residual fragments in a further 38.8% of the cases. The majority of cases of big stones in voluminous hydronephrotic kidneys, usually considered not eligible for ESWL, were successfully managed by ESWL (Figures-1 and 2). The most common complication in our patients was acute pyelonephritis, which almost always occurred after dislodgment of the double-J stent. This is one of the disadvantages of the ambulatory regimen, as patients do not always follow the instruction of returning immediately to our center if some complication occurs.

Using an ambulatory regimen with short fragmentations, the number of sessions is higher but, on the other hand, the number of severe complications may be decreased, and almost all patients can go back to work on the day after the treatment. Besides, using short fragmentation with a piezoelectric lithotriptor and an interval of 2 weeks between the sessions, the probability of functional damage over the kidney is very small, since several papers in which a more powerful lithotriptor (Dornier HM3) was employed conclude that ESWL is harmless for the kidney (4-7). Figure-1 refers to a patient with a recurrence of staghorn calculi after two bilateral pyelonephrolitotomies, to whom any kind of treatment was denied in another center. This patient was submitted to 18 sessions in the right kidney and 14 sessions in the left kidney during 2 years, including 5 short sessions of 20 minutes on the right kidney and four in the left kidney. She was hospitalized during 2 days after the first session, in order to assess its consequences. Thereafter, all the treatments to both kidneys were ambulatory. She only stopped working on treatment days, and during 3 days after a moderate pyelonephritis. The patient referred to in Figure-2, only stopped working on treatment days and had no need for hospitalization. These two examples, like many others included in this series, testify the feasibility of AESWLM for staghorn calculi, even in complicated cases.



**Figure 1** - A) Voluminous recurrent bilateral staghorn calculi in a patient with two previous pyelonephrolithotomies performed three years before; B) IVP showing marked hydronephrosis and a reduction in the renal parenchyma; C) Final result with a little residual fragment in the lower calyx of the left kidney (arrow); D) IVP after treatment showing a marked reduction of the hydronephrosis and a partial recovery in the pyelocalyceal morphology.

As all patients are treated free of costs, we frequently perform short sessions on residual fragments, in order to accelerate their elimination, taking advantage of the recovery of the pyelocalyceal morphology and function (Figures 1-D and 2-D). The patients remain under follow-up, and prevention of recurrences is achieved performing short ESWL sessions whenever a stone is seen. None of the 112 patients that remain under our control developed staghorn calculi. However, as many patients were lost to follow-up, we are unable to know if there was any recurrence of staghorn calculi. We were also unable to correlate the results according to the stone composition, since many patients did not keep the fragments as they were told to. Literature results show that more than half of the patients with staghorn calculi can be successfully managed by ESWL monotherapy, with

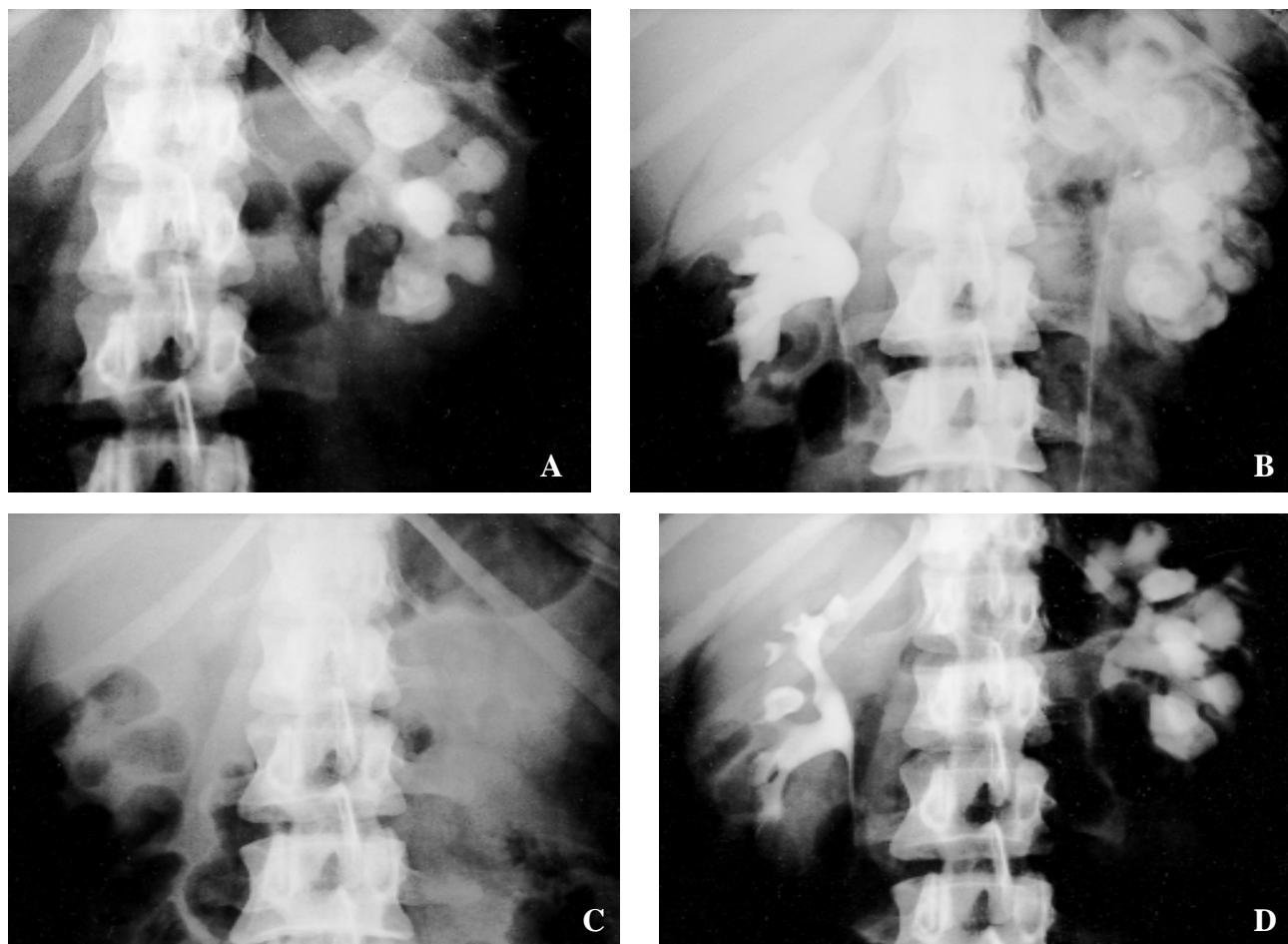
low morbidity (8-14). However, PNL is considered by many as the best treatment option in this setting, either alone or followed by ESWL (10,15-24). One of the claimed advantages of PNL is a shorter treatment time. According to Winfield (19), the cumulative total operative time to debulk staghorn calculi is 3.9 hours for partial ones and 9 hours for complete ones, with an average of 10 days of hospitalization. Given an average ESWL session duration of 60 minutes, these values are roughly equivalent to four and nine sessions, respectively, which is more than what we needed in an outpatient regime (6.1 sessions). However, in most of the papers reviewed by us, there is no detailed reference to the duration of PNL performed by other authors.

A lower rate of ancillary procedures is also claimed in favor of PNL. This observation is mainly

based on series where, the Dornier HM3 lithotriptor's high destructive effect was used to treat the stones on one to three sessions, separated by one to three days and where double J stents were often not placed (10,16,18,19,20,24). The use of double-J stents as a routine and the performance of less aggressive sessions separated by a minimum of 2 weeks (in order to allow a better clearance of fragments between sessions and to give time for renal recovery) reduced the need of auxiliary procedures in our series. On the other hand, the rate of severe complications with PNL is higher and not negligible, even in very experienced hands (10,17,19,20,24,28). The incidence of residual fragments is higher following ESWL than after PNL.

However, the clinical relevance of this fact is not settled. On one hand, most patients with small residual fragments can be considered clinically cured, as they are asymptomatic, and their renal function is unaffected by the small fragments. Furthermore, even in the cases of infected stones, the incidence of subsequent urinary tract infections is unpredictable, and some times not directly related to the presence or absence of fragments, since in many recurrent cases, the bacterial species are not the same (25,26).

On the other hand, the higher risk of stone re-growth from the residual fragments is not as important when dealing with a non-invasive and tolerable therapy (ESWL) as it is when an invasive method



**Figure 2 - A)** Voluminous recurrent staghorn calculi in a patient with a previous pyelonephrolithotomy performed eight years before; **B)** Voluminous hydronephrosis on the IVP with marked reduction in renal parenchyma; **C)** The final result with no residual fragments; **D)** The IVP one year after treatment showing a marked reduction of the hydronephrosis with improvement of the renal function and partial recovery of the pyelocalyceal morphology.

was used. In fact, such re-growths can easily be controlled by short ESWL sessions. In cases where a complete stone clearance is considered necessary, we believe that ESWL should be tried first, and, if residuals remains, PNL with a flexible nephroscope (with which a free stone's rate of about 85% can be obtained may then be used (12,15,27).

This appears to be a much more sensible option than trying PNL in the first place, as more than 50% of patients are rendered totally free of stones with ESWL and can therefore be spared the higher risks of PNL with a high rate of blood transfusions (0.3 to 50%) and their inherent and potential risks of hepatitis and AIDS contamination (10,16-20,24,28,29).

## CONCLUSIONS

1)- Piezoelectric ESWL as ambulatory monotherapy for the treatment of staghorn calculi has shown in our center to be a highly valuable option, affording a 53% stone free rate for an average number of 6.1 sessions per stone, and an overall success rate of 91.8% when kidneys with clinically insignificant residual fragments < 2 mm are included. 2)- The ultrasonic control is a more accurate method to detect residual fragments. 3)- The recurrences of staghorn calculi can be avoided with a close follow-up of the patients, performing ESWL when the residual fragments grow, or when a new small stone appears, as occurred in 68 of the 112 patients under follow-up. 4)- Given the good results obtained in our experience, all staghorn calculi, even massive ones, should be given an opportunity of being treated by ESWL. 5)- In a small number of cases ESWL is ineffective, and these stones have to be treated by invasive techniques.

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## EDITORIAL COMMENT

Whether the author's conclusions are justified depends primarily upon what one is satisfied with. The overall stone-free rate in this series, at 53 percent, is the same as the stone-free rate of 50 percent identified in the analysis of the papers published up to 1993 reported in the AUA Guidelines Report on the Management of Staghorn Calculi. Those 50 percent results were achieved using, for the most part, an unmodified HM-3, a very different and considerably more powerful machine than the Piezoelectric lithotrite used in this study. Most people regard being stone free as the sine qua non for the management of infected stones. I do not believe that the authors have made the case that leaving these patients with stony infected stony material behinds represent a satisfactory option in the average patient, although I would certainly concede that there are occasional patients in whom even residual stones may represent a distinct improvement over the original staghorn status.

There is no unanimity of opinion as to what a "clinically insignificant fragment" is. This disagreement extends not only to the size of such fragments, but to the numbers of such fragments and the only unquestioned and incontrovertible, widely accepted, way to measure "success" and "cure" are stone-free rates. The reality is that the stone-free rates in this study are unimproved over the last 15 years, and it has taken using this lithotrite longer to achieve these

results. Further, many of these patients were unfortunately lost to follow-up, and while I believe that it is safe to assume that most of these stones were struvite stones, the stone analysis was apparently not available in many of these patients.

I certainly respect that treatment of these patients is free to the patient, yet it is nevertheless true that such shock wave treatment still represents a cost center somewhere in the medical system, even if this may be buried in the budget of the National Health Service. Such large numbers of treatment must have some morbidity physically or psychologically in the patient population. As I read this paper, while I am enormously impressed with the large number of patients seen, the reality is that many of these patients were unavailable for follow-up and that of the ones that were residual stones grew and new stones appeared in some 50 percent of the patients treated.

My own view is that this group of patients would have been better being treated in a percutaneous-based practice where the stone-free rate would have been far higher and obtained far more expeditiously. That while percutaneous surgery has its own risk, the stone-free state could be achieved without the multiple treatments, double-J stent placement, and risks of sepsis that attended this group.

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## EVALUATION OF RESIDUAL STONES FOLLOWING PERCUTANEOUS NEPHROSTOLITHOTOMY

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### ABSTRACT

Percutaneous nephrostolithotomy (PCNL) constitutes first line therapy for large and complex renal calculi. However, retained calculi generated by intracorporeal lithotripsy remain a concern because of their potential for growth and future symptoms. Liberal use of flexible nephroscopy identifies residual calculi and increases stone free rates. However, historically the sensitivity of radiographic imaging studies to predict the outcome of flexible nephroscopy has been inadequate. With new, helical, computed tomography (CT) technology, post-PCNL imaging can accurately and reliably detect residual calculi and predict the outcome of flexible nephroscopy, thereby allowing the selective use of second look flexible nephroscopy, and reducing cost and patient morbidity. We review the current recommendations for post-PCNL imaging.

**Key words:** urolithiasis; kidney calculi; nephrostolithotomy, percutaneous; helical CT

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### INTRODUCTION

Percutaneous nephrostolithotomy (PCNL) has become the treatment of choice for large or complex stones. The advantage of PCNL over other noninvasive or minimally invasive treatment modalities is the ability to rapidly and completely clear a large stone burden without the attendant risks and uncertainty associated with fragment passage. Like other minimally invasive modalities, however, PCNL often requires stone fragmentation to enable removal through a 1-centimeter incision. As such, the potential for leaving residual stones is greater with modalities requiring lithotripsy than after intact removal. Indeed, with the advent of shock wave lithotripsy (SWL), the definition of "success" was modified to include "clinically insignificant residual fragments" based on the assumption that these fragments had a high likelihood of spontaneous passage and a low probability of causing symptoms.

The completeness of stone clearance following PCNL, however, is an ongoing concern. A recent review of patient outcomes following SWL suggested that even small residual stone fragments predispose

patients to early symptom recurrence and decreased quality of life (1). Similar outcomes can be expected after PCNL when intracorporeal lithotripsy is used. Unfortunately, the presence of residual fragments following PCNL is not accurately predicted by either plain abdominal radiographs or nephrotomograms (2). Thus, many centers have routinely performed second look flexible nephroscopy to assure a stone-free state after PCNL. Advanced radiographic imaging techniques such as non-enhanced, helical, computerized tomography (CT) have significantly improved the accuracy and reliability of radiographic evaluation of residual stones (3,4). Consequently, the efficacy of percutaneous stone removal is enhanced by careful postoperative radiographic evaluation and selective adjuvant surgical intervention. We review the indications and methods of evaluating for the presence of residual stones following PCNL.

### IMPORTANCE OF A STONE-FREE STATE

Historically, the goal of surgical intervention for stone disease was complete stone removal, and thus the presence of any residual calculi indicated

failure of the procedure. With the introduction of SWL, however, the presence of small residual fragments after treatment was assumed to be inconsequential and thus was considered acceptable. A recent study addressed the fate of residual stone fragments after SWL and found that small residual stones were frequently associated with future stone problems. Streem et al. evaluated 160 patients with  $\leq 4$  mm residual stone fragments at a mean of 23 months post-SWL and found that 43.1% of patients experienced a symptomatic episode or required intervention at an average of 26 months postoperatively (1). Zanetti et al. likewise noted a 22% incidence of symptomatic episodes within 2 years in a group of 129 patients left with  $\leq 4$  residual fragments after SWL (5).

A number of investigators have noted that patients with residual stones have a higher rate of new stone formation than patients rendered stone free after surgery. Graff et al. reported a 6.2% incidence of stone recurrence after SWL in patients rendered stone free versus a 17.2% recurrence rate in patients with residual stones at an average follow-up of 19.1 months post-SWL(6). Likewise, Newman et al. found that 1 year after SWL, 8.4% of stone free patients developed new stones compared with 21.6% of patients with residual stones who demonstrated new stone growth (7). Zanetti et al. followed 88 patients with residual fragments after SWL and found that at a mean follow-up of 42 months, 65% of patients demonstrated stone growth (8). Yu et al. evaluated 94 patients (106 renal units) at a mean of 75.8 months post-SWL.(9) Among 62 renal units free of stone at 3 months, 79% remained stone free and new stone growth occurred in 21% at long-term follow-up (mean 30.5 months). In contrast, among the 44 renal units with residual stones at 3 months, new stone growth ultimately occurred in 70% of cases. Interestingly, a comparison of stone recurrence rates at 1 and 2 years post-surgery in 298 patients rendered stone free after SWL and 62 patients stone free after PCNL with intact stone removal revealed a higher rate of new stone formation in the SWL group (22.2% at 1 year, 34.8% at 2 years) versus the PCNL group (4.2% at 1 year, 22.6% at 2 years), suggesting that residual "dust" after SWL that may not be identifiable on standard radiographs places patients at higher risk for stone recurrence than

when the stone is removed in intact without the potential for residual fragments (10).

Although medical therapy has been shown to reduce the incidence of stone recurrence after SWL, patients with residual fragments remain at higher risk for recurrence compared with patients rendered stone free. Fine et al. retrospectively reviewed stone recurrence rates in 25 patients with ( $n = 13$ ) or without ( $n = 12$ ) residual stones treated with medical therapy after SWL (11). At a mean follow-up of 43.2 months, the group with residual stones demonstrated a higher rate of stone recurrence (median 0.47 stones per patient per year) than the group rendered stone free (median 0.09 stones per patient per year).

Incomplete clearance of infection stones poses a particularly high risk for new stone growth as well as a risk of recurrent infection. Zanetti et al. noted persistent urinary tract infections at a mean follow-up of 42 months in 16% of 250 patients treated with SWL; among those patients with recurrent infection, stone re-growth occurred in 74.4% (8). Beck & Riehle found similar results in a group of 33 patients with struvite stones. At a mean of 26.6 months post-SWL, 77.7% of 18 renal units with residual fragments demonstrated stone re-growth versus 20% of 20 renal units rendered stone free; only 1 patient rendered stone free developed recurrent infection compared with 47% of patients left with residual stone fragments (12). These studies underscore the importance of a stone free state in prevention of infection and stone recurrence in this select group of stone formers.

## RADIOGRAPHIC EVALUATION OF RESIDUAL STONES

Traditionally, post-PCNL radiographic imaging studies have been used to detect residual stones and determine the need for secondary procedures to achieve a stone free state. However, imaging modalities differ in their ability to detect residual stones, and consequently a determination of "stone free" varies according to the imaging modality used. Plain abdominal radiographs are notoriously insensitive for detecting small stones; overlying bowel gas, bony structures and obesity all reduce the sensitivity of plain films for detecting small stones. The use of plain

nephrotomograms increases the sensitivity by eliminating extra-renal structures that obscure renal calculi. A number of investigators have reported a higher stone detection rate with plain nephrotomograms compared with plain abdominal radiographs; in 12% (7/60)(13), 39% (11/28) (14) and 47% (46/98)(15) of patients, respectively, a greater number of stones were detected by nephrotomograms than by plain film radiographs.

Denstedt et al. confirmed improved stone detection rates with nephrotomograms compared with plain abdominal radiographs but found that direct endoscopic inspection was superior to either radiographic imaging technique for detecting residual stones after PCNL (2). In 29 patients with  $\geq 3$  cm renal calculi undergoing PCNL, plain films documented residual stones in 34% of patients, nephrotomograms in 52% and flexible nephroscopy in 69% of patients. Consequently, the use of second look flexible nephroscopy was recommended as a routine adjunct to maximize the efficacy of PCNL, independent of radiographic findings.

The application of non-enhanced CT imaging post-PCNL further improved the ability to radiographically detect residual stones after surgery. Marberger et al. demonstrated small calcifications on CT that were not detected by plain radiographs in 11% of 62 patients 12-43 months after PCNL (16). Likewise, Lehtoranta et al. showed superiority of conventional CT over plain film radiography, nephrotomography and renal sonography in detecting residual stones after PCNL (17). Among 35 patients (36 renal units) evaluated 12 to 36 months post-surgery, stone free rates of 47% by CT, 56% by plain films, 58% by nephrotomograms and 72% by sonography were reported.

Waldmann et al. recently reviewed their experience using CT as the sole imaging modality for detecting residual stones after PCNL (4). Among 124 renal units, post-procedure CT demonstrated retained calculi in 41% of cases. The need for further therapy to retrieve residual stones was based on the volume of retained calculi; 23 patients subsequently underwent flexible endoscopy, 8 patients were treated with SWL, and 21 patients were managed conservatively. The authors concluded that, based on CT findings,

routine second look flexible nephroscopy in all patients would have resulted in a 75% rate of unnecessary surgery. However, the definitive assessment of residual calculi by flexible nephroscopy was not routinely performed in all cases and therefore the true sensitivity of CT and need for an adjunctive procedure could not be assessed.

Non-contrast, thin-cut, helical CT has replaced the intravenous urogram as the imaging modality of choice for detecting ureteral calculi in patients presenting with acute flank pain (18-21). In contradistinction to conventional CT, the use of overlapping image reconstruction allows for precise identification of even small ureteral calculi, and the rapid image acquisition reduces artifact due to respiration variation, further increasing sensitivity.

Applied to the kidney, this technology provides an exceedingly sensitive means of detecting retained calculi after PCNL. Pearle et al. evaluated the sensitivity of plain film radiography and non-enhanced, helical CT in predicting residual stone fragments after PCNL using flexible nephroscopy as the "gold standard" for detecting retained calculi (3). A total of 36 patients (41 renal units) with stones  $> 3$  cm in diameter underwent post-operative imaging with plain film radiographs and non-contrast, thin-cut (5 mm) helical CT, then returned to the operating room for flexible nephroscopy on postoperative day 2 or 3. The number of stones detected by each modality was recorded and compared. An overall stone free rate of 92.6% was achieved after flexible nephroscopy. On average, 0.7, 3.4 and 2.3 stones per renal unit were detected by plain film, CT and flexible nephroscopy, respectively. CT missed no stones detected by flexible nephroscopy. Sensitivity and specificity for the imaging modalities were 46% and 82%, respectively, for plain film radiographs and 100% and 62%, respectively, for CT. Consequently, selective use of flexible nephroscopy after PCNL based on positive CT findings in this series would have avoided an unnecessary operation in 20% of patients. Indeed, this strategy of selective use of flexible nephroscopy would translate into cost savings of \$109,687 per 100 patients at their institution compared with a strategy of flexible nephroscopy in all patients.

## CURRENT RECOMMENDATIONS

While second look flexible nephroscopy remains the “gold standard” for evaluation of residual fragments following PCNL, non-enhanced, helical CT accurately predicts the outcome of flexible nephroscopy and best selects patients who would benefit from repeat surgical evaluation. Furthermore, CT in conjunction with antegrade nephrostogram provides an accurate “road-map” with which to precisely locate residual stones at flexible nephroscopy. We recommend that patients with large stones requiring fragmentation at PCNL who constitute a high-risk group for residual fragments undergo non-contrast, thin-cut (5 mm) helical CT and antegrade nephrostogram on the first post-operative day to identify those patients who would benefit from second look flexible nephroscopy.

In patients with residual stones, flexible nephroscopy is performed on post-operative day 2 to retrieve residual fragments. If the antegrade nephrostogram demonstrates good antegrade drainage and the urine is relatively clear at the time of flexible nephroscopy, the nephrostomy tube is removed and the patient is discharged home. Occasionally tiny fragments are identified on CT that are not identified endoscopically and are presumed to have passed or to be located submucosally. In these cases, flexible nephroscopy is performed unnecessarily (15%). However, this low false positive rate assures that no significant stones are missed.

A policy of selective use of flexible nephroscopy based on positive CT findings will maximize stone free rates while avoiding unnecessary procedures in the majority of patients.

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## INTRACORPOREAL HOLMIUM:YAG LASER LITHOTRIPSY - CURRENT STAGE

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### ABSTRACT

Since Mulvany and Beck first description of Ruby laser for lithotripsy, urologists have been exploiting every possible application of this technology. Relevant to urology is the recently developed Holmium:YAG laser with both soft tissue and lithotripsy applications. The Holmium:YAG laser can effectively fragment calculi of all compositions mainly through a photothermal mechanism. This mechanism result in fewer migrated and smaller stone fragments, compared to electrohydraulic lithotripsy, mechanical lithotripsy or pulsed dye lasers. Because the Holmium:YAG laser can be carried through small flexible quartz fibers, it is ideally suited for the use through small-diameter flexible ureteroscopes in the upper urinary tract. We here provide a comprehensive revision of basic concepts as wavelength, absorption coefficient, chromophores, pulsed laser and the photothermal mechanism of the Holmium:YAG laser lithotripsy. Security concerns, the impact of energy and frequency settings, as well as the influence of different fiber types and its diameters on stone fragmentation are analyzed. The clinical Holmium: YAG laser lithotripsy applications and the series reporting their use are reviewed.

**Key words:** laser; holmium:YAG; lithotripsy  
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### CONCEITOS BÁSICOS EM LASER RELACIONADOS À LITOTRIPSIA

#### Comprimento de Onda

O laser é um feixe de luz intenso. A luz, por sua vez, é uma radiação eletromagnética. Essa radiação exibe as características de uma onda. O comprimento dessa onda é definido pela distância medida entre duas cristas consecutivas. O comprimento de onda define basicamente as características de interação de um laser com as diversas substâncias e tecidos. Como todas as ondas que compõe um feixe de laser possuem o mesmo comprimento de onda (luz monocromática), a interação do laser com as diversas substâncias e tecidos se dá de forma altamente específica (1).

#### Coeficiente de Absorção

Cada laser, dado o seu comprimento de onda, tem a sua energia absorvida de forma diferente por cada diferente substância ou tecido. Existem alguns

tipos de laser que são fortemente absorvidos pela água. Esta interação é importante uma vez que a água predomina na grande maioria dos tecidos. Um laser que seja altamente absorvido pela água apresentará como característica uma baixa penetração nos tecidos em geral produzindo ablação (corte e vaporização) dos tecidos de excelente qualidade sem a ocorrência de lesões térmicas causadas aos tecidos vizinhos. Outros tipos de laser são altamente absorvidos por certos pigmentos ou proteínas teciduais. Essas substâncias são ditas cromóforos desse laser. São exemplos de cromóforos a hemoglobina e a melanina. Um laser que possua como cromóforo a hemoglobina, produzirá coagulação de excelente qualidade (1).

#### Laser Pulsado

Os lasers podem funcionar em modo contínuo ou pulsado. No modo contínuo pode ocorrer um excessivo aquecimento da região tratada resultando em lesões térmicas indesejáveis. No modo pulsado, o feixe de luz é transmitido de forma não contínua, pro-

duzindo uma seqüência de “flashes” separados por curtíssimos intervalos de tempo. Nessa forma de uso do laser, uma energia dezenas de vezes maior que a utilizada na forma contínua pode ser aplicada. Paradoxalmente não ocorre lesão térmica porque a elevada energia transmitida por esse pulso provoca ablação instantânea do tecido. A ablação instantânea remove os restos de tecido antes que eles possam transmitir, por condução térmica, o calor aos tecidos vizinhos (1).

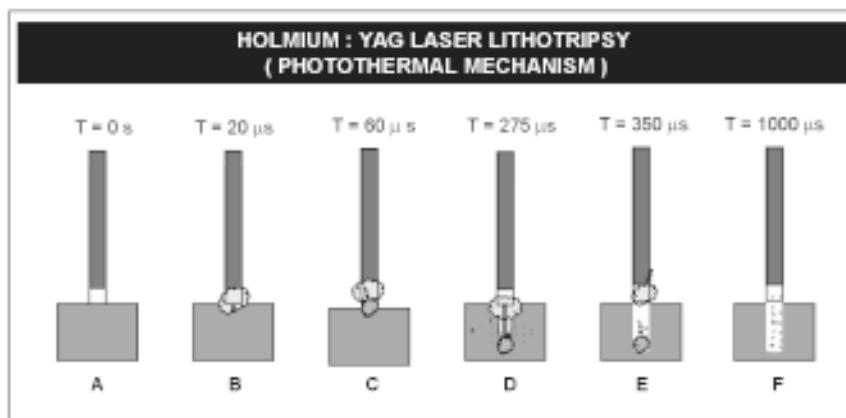
## O LASER HOLMIUM:YAG

O laser Holmium:YAG (Ho:YAG) representa o mais recente avanço em litotripsia intracorpórea. Em 1992, Johnson constatou pela primeira vez a eficácia do laser Holmium:YAG na fragmentação de cálculos de diferentes tamanhos e composições (2). O laser Ho: YAG (Holmium:Yttrium Aluminum Garnet) é um laser com comprimento de onda de 2100 nanômetros (nm). O laser Ho: YAG opera em modo pulsado. Funciona com duração de pulso longa, de 350 a 700 microsegundos ( $\mu$ s). Ele pode fornecer energias de pulso variando entre 0.2 a 3 Joules (J) e

freqüências entre 5 a 20 Hertz (Hz). É fortemente absorvido pela água, tornando-o efetivo e seguro para a realização de ablação na grande maioria dos tecidos com mínima lesão térmica causada aos tecidos vizinhos. Pode ainda ser efetivamente utilizado em ambientes submersos por qualquer tipo de líquido incluindo a urina. O laser Ho: YAG é efetivo para todos os tipos de cálculo, incluindo-se os cálculos de cistina, bruchita e de oxalato de cálcio monohidratado.

## O Mecanismo Fototérmico de Litotripsia do Laser Ho: YAG

A fragmentação de cálculos pelo laser Ho: YAG se dá de forma semelhante a uma “perfuração por broca”. Os cálculos são reduzidos a poeira fina, areia e pequenos fragmentos (3). Através do uso de fotografia de alta velocidade e medida de pressão acústica junto ao cálculo durante a litotripsia, foi demonstrado que o laser Ho: YAG é altamente absorvido pela água e também por todos os materiais constituintes dos cálculos, sem exceção (4). Por causa de sua alta absorção pela água, imediatamente após a sua emissão, o feixe de laser vaporiza a mesma, pro-



**Figure 1 -** Ho:YAG laser lithotripsy (lithotripsy at normal incidence). A)- the output end of the optical fiber is placed in contact with the stone surface; B)- vapor bubble begins at 20 ms; C)- lithotripsy begins at 60 ms (gray area near stone surface); D)- fragment ejection and vapor bubble continue at 275 ms; E)- pulse ends, stone ejection continues and vapor bubble is asymmetric; F)- gas bubbles are floating up from stone surface.

Esquema ilustrativo de litotripsia com laser de Holmium:YAG (incidência do feixe normal à superfície do cálculo). A)- a fibra do laser é posicionada em contato com a superfície do cálculo; B)- inicia-se a formação de uma pequena bolha de cavitação assimétrica junto à ponta da fibra (cinza claro); C)-formação de um “canal de vapor” que serve de meio de condução ao laser até à superfície do cálculo (“Efeito Moses”) e início da litotripsia (área cinza escura junto à superfície do cálculo); D)- ejeção de fragmentos finos (“efeito de broca”) e a bolha de cavitação presente; E)- aos 350 ms termina o pulso do laser, mas a ejeção de fragmentos ainda continua; F)- bolhas de gás flutuam a partir da superfície do cálculo.

duzindo uma pequena bolha de cavitação (Figura-1). Esse mesmo vapor e a longa duração do pulso desse laser dão origem a um segundo fenômeno, conhecido como “Efeito Moses” (5). O vapor d’água absorve 10.000 vezes menos a energia do laser Ho: YAG do que a água em estado líquido. Como a energia do laser em meio ao vapor não é prontamente absorvida, o feixe de luz avança formando um “canal de vapor” que serve de meio de condução ao laser até sua chegada à superfície do cálculo. A energia assim conduzida e o vapor gerado ao redor do feixe dão um aspecto alongado e assimétrico à bolha de cavitação. A expansão e subsequente colapso dessa bolha resulta em uma onda de choque acústica de baixa intensidade que não é suficiente para produzir a fragmentação ou mesmo provocar a migração do cálculo. Através da fotografia de alta velocidade também se verificou que a litotripsia ocorre já com 60 µs, muito antes do colapso da bolha de cavitação. A exposição do cálculo à energia do laser Ho: YAG é tanto maior quanto menor é a distância da ponta da fibra à superfície do cálculo. Por esse motivo, a litotripsia com laser Ho: YAG é realizada posicionando-se a fibra em contato (“laser de contato”) com a superfície do cálculo (5). Demonstrou-se uma perda de massa significativamente maior nos cálculos (de todas as composições) submetidos à litotripsia em condições normais de temperatura do que em cálculos congelados submetidos à litotripsia. Também se verificou maior perda de massa em cálculos submetidos à litotripsia na presença de ar do que em cálculos submetidos à litotripsia em meio líquido (resfriados pela irrigação). Os produtos recuperados de cada cálculo após a litotripsia, em todos os casos, corresponderam a produtos de degradação térmica dos materiais inicialmente constituintes do cálculo.

Foi ainda demonstrado que, em geral, o efeito de vaporização do cálculo dado pelo laser Ho: YAG é tanto maior quanto mais baixa é a temperatura de fusão dos materiais constituintes desse cálculo (6).

Devido ao mecanismo de ação fototérmico do laser Ho: YAG o problema da retropulsão durante a litotripsia não ocorre. Foi demonstrado em estudo experimental que a retropulsão do cálculo pelo uso do laser Ho: YAG só ocorre quando são utilizadas baixas densidades de energia (baixos níveis de ener-

gia de pulso em associação com fibras de maior diâmetro). Essa situação não se reproduz na prática uma vez que nessas condições a litotripsia com o laser Ho: YAG não ocorre (7).

### **Fibras de Quartzo, Níveis de Energia e Freqüência de Pulso**

Comprimentos curtos de onda, compondo o espectro de luz visível e próximo ao infravermelho (de 300 a 2100 nm) permitem ao laser ser transmitido através de fibras. As fibras utilizadas em associação com o laser Ho: YAG são fibras de quartzo de baixo teor de água especialmente revestidas, para evitar a absorção da energia do laser pela água.

A seleção apropriada da fibra, nível de energia e freqüência do pulso otimizam o resultado da litotripsia e minimizam despesas com material. Fibras de menor diâmetro, de 200 ou 365 micrômetros ( $\mu\text{m}$ ), em combinação com ureteroscópios semi-rígidos e flexíveis devem ser usados no tratamento de cálculos do trato urinário alto.

As fibras de 365  $\mu\text{m}$  devem ser usadas no tratamento dos cálculos ureterais onde mínimas deflexões do ureteroscópio são necessárias para a litotripsia nessas condições. Como as fibras de 200  $\mu\text{m}$  são mais caras, seu uso deve ser reservado para a fragmentação do cálculo intra-renal, especialmente para o cálculo de cálice inferior, onde se requer a máxima deflexão do ureteroscópio flexível. As energias ideais para as fibras pequenas (200 e 365  $\mu\text{m}$ ) são sempre inferiores a 1.0 J com freqüência variando de 5 a 10 Hz (8).

As fibras maiores (550 e 1000  $\mu\text{m}$ ) podem ser usadas no tratamento de cálculos renais (por via percutânea) ou vesicais, onde não há necessidade de grandes deflexões das mesmas. A fibra de 550  $\mu\text{m}$  deve ser a preferida nessas condições por ser comparável em eficácia à fibra de 1000  $\mu\text{m}$  e por ser mais barata. A energia empregada pode ser de até 2.0 J com freqüências de até 15 Hz sem ocorrência de dano à fibra. Deve-se notar que durante o emprego de altas freqüências a visibilidade do procedimento pode ser afetada.

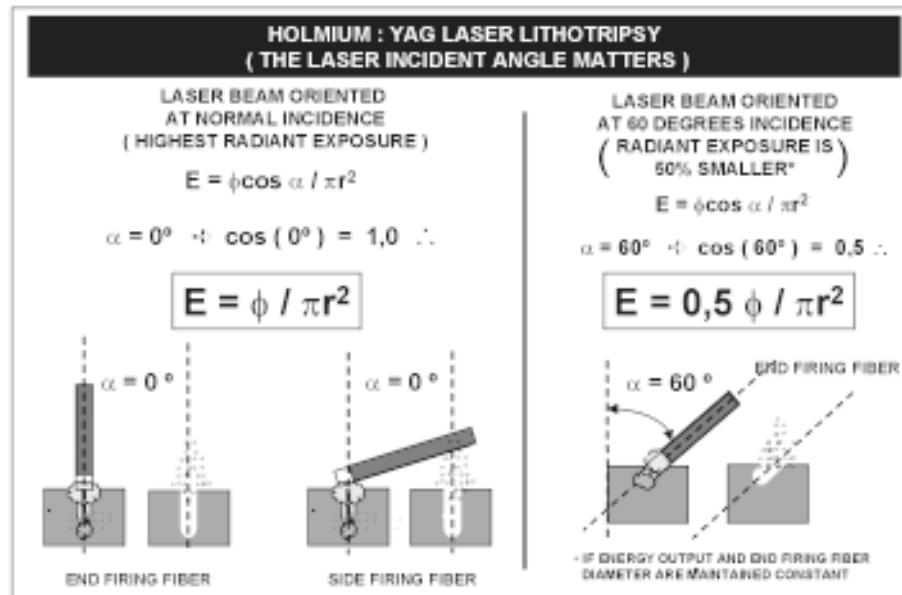
A emissão do laser na extremidade distal da fibra pode se dar lateralmente (“side firing”) ou em continuação ao eixo longitudinal da fibra (“end firing”). O ângulo de incidência do feixe de laser Ho:

YAG sobre a superfície do cálculo interfere na eficiência da litotripsia (Figura-2). Foi verificado que o uso de fibras “side firing” produz velocidade de fragmentação maior do que as fibras “end firing” para tratamento de cálculos renais por via percutânea e para tratamento de cálculos vesicais por via transuretrral (9 e 10). Essa constatação prática deriva do comportamento do laser Ho: YAG expresso pela fórmula  $E = \Phi \cos(\alpha) / \pi r^2$ , onde “E” representa a exposição do cálculo à energia do laser (medida em Joules / cm<sup>2</sup>), “Φ” representa a energia do pulso do laser (medida em Joules), “α” é o ângulo de incidência do feixe de laser em relação à superfície do cálculo e “r” representa o raio da área de contato gerada pelo feixe de laser sobre a superfície do cálculo. Disso resulta que para um ângulo α igual a 0° (incidência do feixe normal à superfície do cálculo) obtém-se efeito de fragmentação máxima ( $\cos 0^\circ = 1$ ) e para um ângulo de 60°, obtém-se uma perda de efeito de fragmentação de 50% ( $\cos 60^\circ = 1/2$ ) quando comparado à condição anterior (Figura-2). Foi observado

que no tratamento de cálculos vesicais, a fibra “end firing” tende a orientar o feixe de forma a atingir mais tangencialmente a superfície do cálculo. Na via retrógrada e para o reduzido espaço intra-renal isso também ocorre. Com base nessas observações demonstrou-se clinicamente que o uso de uma fibra do tipo “side firing” de 70° oferece maior liberdade e controle no posicionamento do feixe em incidência mais normal à superfície do cálculo levando a velocidades de fragmentação significativamente maiores (10).

### O Uso de Guias Durante a Litotripsia com o Laser Ho:YAG

Nenhum guia é imune a ação do laser Ho: YAG quando ocorre contato do feixe de laser com o mesmo. A integridade do guia deve ser sempre observada evitando-se o abandono de fragmentos do mesmo no interior do sistema coletor após a conclusão do procedimento. Em geral, a energia requerida para induzir um defeito ou corte ao guia é superior àquela necessária para a realização da litotripsia



**Figure 2 - Ho:YAG laser lithotripsy.** Laser fiber is oriented at normal incidence ( $\alpha = 0^\circ$ ) yielding the highest energy density and maximum lithotripsy. When the incident angle is 60 degrees, laser energy is spread over large surface resulting in low energy density and reduction of lithotripsy in 50% (if energy output and fiber diameter are maintained constant).

**Litotripsia com laser de Holmium:YAG.** Feixe de laser incidindo em posição normal à superfície do cálculo obtém-se o efeito máximo de litotripsia (tanto para as fibras “end firing” como para as “side firing”). Para uma inclinação do feixe de laser de 60° em relação à superfície do cálculo ( $\alpha = 60^\circ$ ), ocorre uma redução do efeito de litotripsia de 50% (se mantidos constantes o nível de energia do pulso e o diâmetro da fibra).

(quando se observa a distância mínima de 1 mm entre a fibra e o guia). Guias revestidos de “PTFE” ou outros materiais parecem não oferecer maior proteção aos efeitos do laser (11).

### Questões de Segurança

Para evitar-se lesões às paredes do urotélio, dois cuidados básicos devem ser tomados: o posicionamento acurado da fibra e um campo de visão livre (12). Por causa do “efeito de broca” do laser, muito cuidado deve ser tomado para que não ocorra a transfixação do cálculo pela fibra com lesão de estruturas localizadas posteriormente ao mesmo (3). A fibra também deve ser mantida 5 mm à frente da ótica do aparelho para evitar danos à lente do mesmo. A distância de 1 mm da mucosa já é suficiente para evitar a ocorrência de lesões à mesma (4). A luz do laser Ho: YAG apresenta afinidade por cromóforos presentes na córnea e retina do olho humano que suscitam a necessidade do emprego de óculos de proteção. Os óculos de proteção do laser de Ho: YAG filtram simultaneamente comprimentos de onda inferiores a 310 nm e superiores a 825 nm (abaixo e acima do espectro de cores visível ao olho humano). Dessa forma, os óculos de proteção do laser de Ho: YAG não interferem na percepção das cores pelo cirurgião (13).

Outra questão de segurança envolvendo o laser Ho: YAG diz respeito ao tratamento dos cálculos de ácido úrico. Sabe-se que o cianeto pode ser produzido a partir do aquecimento de ácido úrico. Estudando-se experimentalmente a litotripsia do cálculo de ácido úrico pelo laser Ho: YAG foi demonstrada a produção, entre outras substâncias, de cianeto e de ácido cianúrico (5,14). A dose letal de cianeto por via oral é de 50 mg. Para obter-se essa quantidade a partir do aquecimento de ácido úrico seria necessário empregar mais de 100 KJ de energia com um laser de Ho: YAG, circunstância que provavelmente não se verifica na prática. Mesmo assim, é recomendado ter em mente a possibilidade dessa complicaçāo durante o tratamento de cálculos de ácido úrico mantendo-se os devidos cuidados em relação ao paciente, pessoal médico e recursos de tratamento frente a uma eventual intoxicação por cianeto.

### Complicações pelo Emprego do Laser Ho: YAG

Complicações com o uso do laser Ho:YAG tem sido poucas e principalmente devidas ao uso inapropriado do ureteroscópio, dilatadores e guias ou a incapacidade de acessar o cálice inferior através da ureteroscopia flexível (3,15-17).

### Litotripsia Intracorpórea com Laser Ho:YAG - Resultados Clínicos

Foi demonstrado que a litotripsia com laser Ho:YAG resulta em fragmentos menores que aqueles obtidos com o uso dos litotritores balístico, eletrohidráulico ou laser “pulsed dye”, não importando o tamanho ou a composição do cálculo (9).

Os resultados de litotripsia com o laser Ho:YAG para cálculos ureterais são excelentes sendo que alguns autores chegam a apontá-lo como tratamento de primeira escolha para os cálculos de ureter distal. Quando considerado o tratamento de cálculos de qualquer localização, tamanho ou composição, as taxas de sucesso superaram os 90% (3). Os casos não resolvidos, em geral, são devidos a problemas não relacionados ao laser, mas antes relacionados à localização do cálculo ou a dificuldade em acessá-lo (estenose ureteral e alterações anatômicas).

Na via retrógrada, a ureteroscopia associada ao uso da fibra de 200 µm demonstrou ter enorme utilidade e eficácia (3,18).

Utilizando-se exclusivamente ureteroscópio flexível e laser Ho:YAG por via retrógrada em 303 pacientes, obteve-se sucesso no tratamento de 97% dos casos de cálculo ureteral e de 79% dos casos de cálculo intra-renal. Quando o tratamento do cálculo de trato urinário superior foi realizado em 2 tempos cirúrgicos, a taxa de sucesso aumentou para 91% (17).

Quando considerada a aplicação do laser Ho:YAG ao tratamento de cálculos urinários em geral (por via retrógrada ou anterógrada) os resultados demonstraram ser altamente satisfatórios. Numa série de 210 pacientes, foram tratados cálculos de todos os tipos de composição. De 109 cálculos ureterais, 106 foram tratados por via retrógrada com sucesso em 97% dos casos após um único procedimento. De 113 cálculos renais, 99 foram tratados por via retrógrada e destes, 79 (80%) foram tratados em uma úni-

ca sessão. A combinação com a ureteroscópia flexível (com deflexão ativa) permitiu o tratamento de 38 cálculos de cálice inferior (de um total de 45 casos) resultando em taxa de sucesso de 84%. O sucesso para tratamento de cálculos intra-renais independentemente de seu tamanho, formato ou posição, foi de 90%. Todos os 28 pacientes com cálculos vesicais foram tratados com um único procedimento (19).

Em outra série de 160 pacientes (127 com cálculo ureteral, 18 com cálculo renal e 15 com cálculo de bexiga) resultados semelhantes foram alcançados. Dos 18 pacientes com cálculo renal, 16 foram abordados por via percutânea, sendo que 5 destes (com cálculos de tamanho médio de 3.5 cm) resultaram livres de cálculo após um único procedimento. Os 2 restantes foram tratados por via retrógrada (um cálculo de JUP e um de cálice inferior) também em uma única sessão. Nos 127 pacientes com cálculo ureteral, uma taxa de sucesso de (97%) foi obtida. Todos os 15 pacientes com cálculos vesicais foram tratados em uma única sessão. O autor termina concluindo que o laser Ho:YAG é eficiente, seguro e versátil (12).

## CONSIDERAÇÕES FINAIS

O desenvolvimento da endourologia abriu espaço à utilização do laser. O laser Ho: YAG veio ocupar esse espaço facultando ao urologista o seu emprego no tratamento de afecções cutâneas, estenoses, tumores uroteliais, HPB e litíase urinária. Duas restrições podem ser feitas ao uso do laser Ho:YAG. A primeira, relativa ao custo do equipamento. Se considerado esse equipamento para fins exclusivos de litotripsia, ele pode não se mostrar atraente do ponto de vista de investimento (10). A segunda restrição ao laser holmium:YAG consiste na verificação prática de uma menor velocidade de litotripsia desse equipamento quando comparado aos outros métodos disponíveis. Essa segunda restrição vem sendo superada através da correta utilização das diferentes fibras, bem como do correto ajuste do nível de energia e freqüência de pulso a serem utilizados em cada diferente procedimento.

Do ponto de vista do paciente, o uso do laser Ho:YAG facilita ao urologista o tratamento de casos

clínicos complicados onde a anestesia geral e o sangramento precisam ser evitados. De todos os lasers utilizados em litotripsia, o laser Ho: YAG apresenta as melhores características e resultados.

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## LITHOTRIPSY WITH HOLMIUM:YAG LASER - INITIAL RESULTS

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### ABSTRACT

**Introduction:** The Holmium:YAG laser is the most recent method for lithotripsy of urinary stones, using quartz flexible fibers for its transmission. A vaporization bubble is created on the tip of the fiber when the laser strikes water, fragmenting and vaporizing the stone. We present our initial results with this technique.

**Materials and Methods:** We performed 81 lithotripsies in 75 patients using the Holmium:YAG laser as the only source of energy. Fifty-eight cases of ureteral stones were treated by ureteroscopy and 23 cases of renal stones underwent retrograde nephroscopy (15 cases) and percutaneous nephroscopy (8 cases). We used rigid and flexible ureteroscopes and a flexible nephroscope for the procedures.

**Results:** Ureteral stones were fragmented in 54 cases (93.1%) while we obtained total destruction of 10 (62.5%) intracalyceal stones and 6 (85.7%) pelvic stones after a single session of laser lithotripsy. The complications were 4 ureteral perforations, treated conservatively with double J stents.

**Conclusions:** Holmium:YAG laser is an effective and safe method for treating urinary stones.

**Key words:** lithiasis; lithotripsy; kidney; ureter; laser; holmium:YAG

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### INTRODUÇÃO

O tratamento dos cálculos renais e reterais mudou dramaticamente nos últimos 20 anos. A introdução da litotripsia extracorpórea por ondas de choque (LECO) no tratamento dos cálculos urinários na década de 80 nos trouxe a falsa impressão de que todos os cálculos poderiam ser tratados pelas máquinas. As altas taxas de insucesso da LECO no tratamento dos cálculos ureterais e dos cálculos coraliformes fizeram com que os procedimentos endourológicos continuassem a ter seu espaço. A cirurgia percutânea continua sendo o melhor tratamento para os cálculos renais de grande tamanho e com a ureterorenoscopia obtém-se melhores resultados nos cálculos impactados no ureter. Com o advento do Holmium:YAG laser grande parte dos cálculos urinários podem ser tratados atualmente por via endoscópica. Utilizando fibras flexíveis de quartzo para sua transmissão esse laser quando ativado na

água cria uma bolha de vaporização na ponta da fibra que fragmenta e vaporiza o cálculo.

O objetivo desse trabalho é apresentar os resultados iniciais no tratamento dos cálculos renais e reterais com o uso do Holmium:YAG laser como única fonte de energia.

### MATERIAL E MÉTODOS

Entre dezembro de 1998 e janeiro de 2000 realizamos 81 procedimentos de litotripsia em 75 pacientes portadores de cálculos urinários com o uso do Holmium:YAG laser. Quarenta e dois pacientes eram do sexo masculino (56%) e 33 do sexo feminino (44%). A idade variou de 17 a 61 anos (média de 35.9). Vinte e um pacientes eram portadores de cálculos renais sendo que 2 desses pacientes apresentavam cálculos renais bilaterais e 3 apresentavam cálculos ureterais concomitantes. Cinquenta e quatro pacientes eram portadores de cálculos ureterais sen-

**Table 1 - Location of urinary calculi.***Localização dos cálculos urinários.*

Ureter (n = 58)			Kidney (n = 23)	
Upper	Middle	Lower	Calices	Pelvis
13 (22.5%)	16 (27.5%)	29 (50%)	16 (69.5%)	7 (30.5%)

do que um desses apresentava cálculo ureteral bilateral. A localização dos cálculos ureteral e renal é demonstrados na Tabela-1. Foram tratados cálculos de vários tamanhos sendo que os cálculos ureterais tinham um diâmetro entre 0.7 e 1.7 cm e os cálculos renais entre 0.4 e 2.4 cm.

Os endoscópios utilizados foram um ureteroscópio semi-rígido Storz 27400 CL diâmetro externo de 7.5F, um ureteroscópio flexível Storz 11273 BB com diâmetro externo de 7.5F e um nefroscópio flexível Storz 11001 DD com diâmetro externo de 15F. O acesso ao ureter foi realizado sempre com a dilatação prévia do óstio ureteral, tendo sido utilizados os dilatadores fasciais de Nottingham na maioria das vezes, o balão dilatador em 4 casos e o cateter de dupla luz em outros 3 casos.

Os cálculos ureterais foram acessados pelo ureteroscópio rígido ou flexível com prévia passagem de fio guia hidrofílico. Os cálculos renais foram acessados pelo ureteroscópio flexível ou pelo nefroscópio flexível através de punção percutânea. A anestesia geral foi utilizada para os procedimentos realizados no rim e o bloqueio peridural para os realizados no ureter. A fonte geradora do Holmium:YAG laser foi um aparelho Odissey da Convergent® com 15 watts (W) de potência, com comprimento de onda de 2100 nm, energia do pulso máxima de 3.0 J, duração do pulso de 350 e 700 µs e freqüência de 5 a 15

Hz. As fibras utilizadas foram as de 200 µm para os casos de cálculos em cálices inferiores e as de 400 e 600 µm para todos os outros casos. A aplicação do laser se fez com uma energia que variou de 0.5 a 1.2 J e uma freqüência de pulso entre 5 e 15 Hz. A fragmentação do cálculo iniciava-se pela periferia provocando uma cavitação e posterior pulverização.

## RESULTADOS

Realizamos 81 litotripsias em 75 pacientes utilizando o Holmium:YAG laser como única forma de energia. Os resultados são apresentados na Tabela-2. Foi considerado sucesso quando ocorreu completa fragmentação ou pulverização do cálculo, restando somente fragmentos menores do que 2 mm que saíram com a própria irrigação ou posteriormente com a retirada do cateter duplo J.

Os cálculos renais foram tratados de duas formas, o acesso retrógrado e o acesso percutâneo. A via retrógrada através da ureteroscopia flexível foi utilizada em 15 casos (65.2%) e o acesso percutâneo através do nefroscópio flexível em 8 casos (34.7%). Os cálculos de pelve renal foram completamente fragmentados pelo laser exceto em 1 caso em que devido ao tamanho do cálculo (2.4 cm) optamos por terminar a fragmentação com ultra-som. Dos 16 cálculos intracalicinais ocorreu a completa fragmentação de 1

**Table 2 - Results of Holmium:YAG laser lithotripsy.***Resultado das litotripsias com Holmium:YAG laser.*

Location	Number of Cases	Sucess (n)	Sucess (%)
Renal Pelvis	7	6	85.7
Renal Calices	16	10	62.5
Upper Ureter	16	14	87.5
Middle Ureter	16	15	93.75
Lower Ureter	26	25	96.15

cálculo localizado no grupo superior e de 3 cálculos localizados no grupo médio; sendo que dos 11 cálculos restantes localizados no grupo inferior foi possível a fragmentação completa dos cálculos no interior do próprio cálice em apenas 4 casos. Em 8 casos não conseguimos deflexão suficiente do ureterorenoscópio, após a passagem da fibra do laser pelo seu canal de trabalho, que permitisse o acesso ao cálice; porém em 2 desses casos foi possível a remoção dos cálculos do cálice para a pelve com a ajuda de uma cesta de Dormia fragmentando os cálculos nesse local.

Não ocorreu nenhuma complicação séria em nossa casuística com o uso dessa fonte de energia exceto quatro casos de perfuração do ureter, confirmados pela injeção retrógrada de contraste iodado, todos tratados conservadoramente com a passagem do cateter duplo J que permaneceu por 21 dias.

## DISCUSSÃO

A litotripsia extracorpórea (LECO) veio mudar dramaticamente o tratamento da litíase urinária. Hoje essa modalidade terapêutica está consolidada e suas taxas de sucesso foram comprovadas após estudo conduzido pela Associação Americana de Urologia em 1997, numa meta-análise de todos os artigos publicados desde 1966 (1).

Apesar de altas taxas de sucesso a LECO não se mostra eficaz em todos os casos de cálculos urinários. A cirurgia renal percutânea continua sendo o melhor tratamento para os grandes cálculos renais e com a ureterorenoscopia se obtêm os melhores resultados nos cálculos impactados no ureter (2,3). O desenvolvimento da fibra óptica tornou possível a fabricação de ureteroscópios de diâmetro bastante reduzido, a princípio rígidos, depois semi-rígidos e finalmente flexíveis. Ao mesmo tempo foram desenvolvidos litotridores que empregam variadas formas de energia como a ultra-sônica, a pneumática e a eletrohidráulica.

Mais recentemente o laser passou a fazer parte desse arsenal terapêutico, muito embora essa fonte de energia já venha sendo estudada há mais de 3 décadas. O primeiro relato de fragmentação de cálculo urinário utilizando essa fonte de energia coube a Mulvaney et al. em 1968 com o laser de rubi (4).

Pensel et al. em 1981 descreveram os princípios da fragmentação de cálculos renais com neodymium YAG laser (Nd: YAG) (5). Com esse tipo de laser Watson et al. obtiveram bons resultados na fragmentação dos cálculos urinários, porém com alto índice de lesão ureteral (6).

O Holmium:YAG laser disponível para uso em medicina somente há alguns anos atrás combina um grande poder de fragmentação dos cálculos com uma grande segurança para os tecidos vizinhos. Com um comprimento de onda de 2100 µm esse laser emite energia que varia de 0.5 a 2 J, em pulsos de 350 a 700 µs que instantaneamente transforma água em vapor. Seu mecanismo de ação é fototérmico. Utilizando fibras flexíveis de quartzo para sua transmissão, esse laser quando ativado na água cria uma bolha de vaporização na ponta da fibra que fragmenta e vaporiza o cálculo. O comprimento de onda do Holmium:YAG laser está localizado na região infravermelha do espectro eletromagnético e é fortemente absorvida pela água. A luz do laser penetra apenas 0.5 mm na água ou no tecido porque a água é o cromóforo dominante para a luz do Holmium laser. Fotografias de alta velocidade revelam que uma pequena bolha de vapor é criada quando se inicia o pulso do laser. Sendo um laser de contato, seu efeito térmico somente se faz quando a ponta da fibra encosta na superfície a ser tratada, fato que o torna bastante seguro, pois se aplicado com critério, não provoca dano aos tecidos vizinhos. Quando a ponta da fibra ótica não encosta no cálculo, ou qualquer outra patologia a ser tratada, o meio líquido entre eles é vaporizado, formando um túnel de vapor. Este vapor absorve 10.000 vezes menos a energia do Holmium:YAG laser que a água, no entanto é insuficiente para a fragmentação do cálculo, causando apenas um turbilhão nos fragmentos e no meio de irrigação. Este fato é descrito como efeito “Moses” (7).

Em nossa casuística tivemos 4 perfurações de ureter, todas pequenas e identificadas imediatamente, que foram tratadas conservadoramente com implante do cateter duplo J. As 4 perfurações ocorreram entre os primeiros 20 casos iniciais e deveu-se a aplicação do laser diretamente na parede ureteral edemaciada no local do cálculo. Esse pequeno índi-

ce de complicação mostra e segurança no manuseio dessa fonte de energia.

A eficácia do Holmium:YAG laser nos casos de cálculo ureteral em nossos pacientes foi bastante alta, não importando o tamanho do cálculo. Lee et al. realizaram um estudo comparativo entre a litotripsia pneumática (Lithoclast®) e litotripsia com Holmium: YAG laser (Coherent®), em cálculos ureterais, encontrando uma taxa de pacientes livres de cálculo em 73% com Lithoclast e 96% com Holmium:YAG (8). Nossos índices de sucesso em cálculos ureterais foram bastante altos mesmo nos casos de terço superior. Isso se deve ao fato da fibra de laser poder ser usada em ureteroscópios flexíveis que atingem mais facilmente esse segmento do ureter do que os ureteroscópios rígidos (9). Outro fator importante na comparação com os litotridores pneumáticos é que o laser reduz os cálculos a fragmentos muito reduzidos, alguns são até pulverizados, sem provocar seu deslocamento, ao contrário dos pneumáticos que com o impacto podem provocar a migração do cálculo (10).

Em relação aos cálculos renais nosso índice de sucesso foi bastante alto (85.7%) nos casos de cálculos localizados na pelve e baixo nos cálculos localizados nos cálices(62.5%). Esses resultados são piores do que os descritos na literatura. Grasso et al. obtiveram um índice de sucesso de 79% nos casos de cálculos renais, Bagley et al. descreveram índices superiores a 87% e Travassos et al. uma taxa de sucesso de 99.4 % (9,11,12). Esse mau resultado se deve principalmente ao maior número de cálculos localizados no grupo caliciano inferior. Sampaio e colaboradores descreveram a relação entre o ângulo infundibulo-calicial e a taxa livre de cálculos após sessões de LECO (13,14). Os maus resultados da LECO nos casos de cálculos localizados em cálices inferiores tornaram atraentes os procedimentos endourológicos especialmente com a utilização dos ureteroscópios flexíveis. A limitação desse procedimento, no entanto, está relacionado à anatomia do cálice e à deflexão do aparelho principalmente depois da passagem da fibra de laser pelo seu canal de trabalho. Em nossos casos a perda da deflexão ativa do aparelho depois da passagem da fibra de menor diâmetro (200 µm) impedi a litotripsia no interior

do próprio cálice na maioria das vezes. Em duas situações utilizando-se a deflexão ativa e passiva do aparelho foi possível a remoção do cálculo para outro local permitindo sua fragmentação.

## CONCLUSÃO

Nossos resultados comprovam que o Holmium: YAG laser é uma excelente fonte de energia para utilização na litotripsia intracorpórea.

O fato de poder ser usado em aparelhos flexíveis além de permitir aumentar as taxas de sucesso da litotripsia no terço superior do ureter torna possível o acesso ao interior dos cálices renais. Sua eficácia, versatilidade e segurança aliadas a diminuição do seu custo a cada dia, torna-o hoje uma excelente forma de tratamento para os cálculos urinários.

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## THE INFLUENCE OF AGE AND PROSTATIC VOLUME ON SERUM PROSTATE SPECIFIC ANTIGEN LEVELS IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

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### ABSTRACT

Over the past few years, prostate specific antigen (PSA) has emerged as the best tumor marker for this organ. However, PSA is not cancer-specific and can be elevated in patients with benign prostatic hyperplasia (BPH). In order to better define the influence of BPH on serum PSA levels, blood samples from 146 BPH patients were assayed for PSA and the values were correlated with patient's age and prostate volume. The mean PSA for the age groups 40 to 49 years, 50 to 59 years, 60 to 69 years, and over 70 years were 0.8 ng/ml, 1.7 ng/ml, 3.15 ng/ml, and 4.72 ng/ml, respectively. The increase in PSA levels also paralleled prostate enlargement. Thus, prostate sizes of < 30 g, 30 to 39 g, 40 to 59g, over 60g, corresponded to mean PSA values of 1.58, 2.05, 3.97 and 6.19 ng/ml, respectively. Pearson's parametric correlation for age vs. prostatic volume ( $r = 0.25975$ ,  $p = 0.002$ ), age vs. PSA ( $r = 0.37513$ ,  $p = 0.0001$ ) and prostatic volume vs. PSA ( $r = 0.59784$ ,  $p = 0.0001$ ) were all statistically significant. Approximately 14% of patients presented elevated serum PSA levels, and transrectal ultrasonography guided prostatic biopsy, revealed prostatitis and BPH in 50% of the patients.

In conclusion, there is a marked and statistically significant influence of age and prostate volume on serum PSA levels. The older the patient and the largest his prostate volume, the higher the expected PSA serum level. Another factor that can influence serum PSA levels is the presence of prostatitis.

**Key words:** prostate; prostatic hyperplasia; prostate neoplasms; prostatitis; prostate-specific antigen  
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### INTRODUÇÃO

O antígeno prostático específico (PSA) é uma proteína sérica pertencente à família das calicreínas (1,2). Pode ser produzido tanto pelas células prostáticas epiteliais normais, hiperplásicas e malignas. A sua função no organismo é a lise do coágulo seminal, porém pode elevar-se no sangue devido à ruptura das barreiras biológicas que separam a próstata do sangue (3). Um das causas desta ruptura é o aumento do número das células epiteliais ductais determinadas pela hiperplasia prostática benigna (HPB). A hiperplasia prostática benigna (HPB) é o tumor benigno mais frequente do homem, existindo evidência histológica desta neoplasia em cerca de 40% dos homens aos 50 anos e quase 90% aos 80 anos de idade (4). Stamey et al. (5) demonstraram uma relação linear entre o peso prostático e os níveis sanguíneos do PSA, onde cada

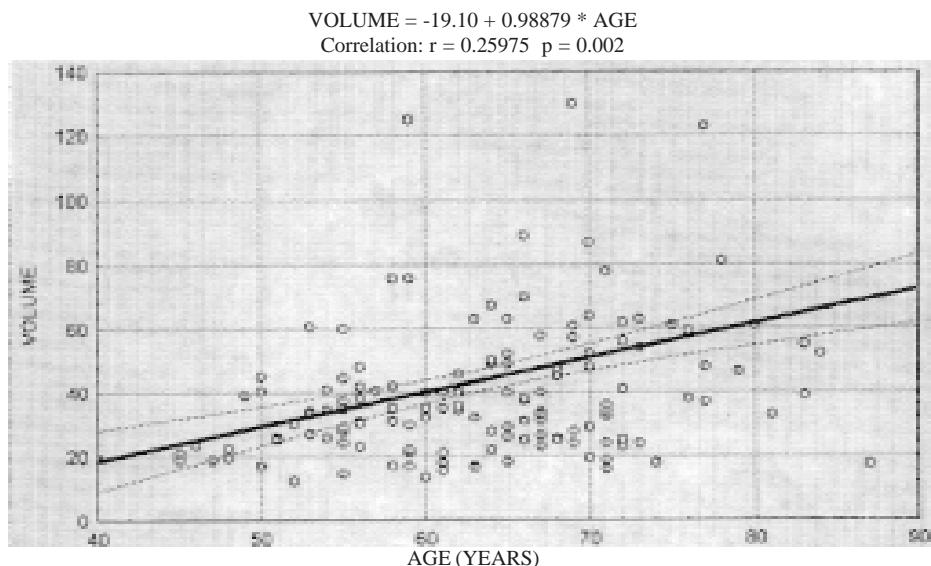
grama de tecido prostático hiperplásico produz cerca de 0.3 ng de PSA no sangue.

Outro fator que pode influenciar os níveis séricos do PSA é o aumento da idade. Oesterling et al.(6) mostraram uma influência forte da idade sobre o PSA, tendo inclusive sugerido a adoção de faixas etárias na interpretação de alterações sanguíneas desta proteína. Diante deste cenário a proposta deste trabalho é analisar o comportamento dos níveis séricos do PSA em um grupo de pacientes ambulatoriais portadores de HPB.

### MATERIAL E MÉTODOS

No período de janeiro de 1996 a fevereiro de 1997 foram estudados 146 pacientes que procuraram o ambulatório de urologia para avaliação prostática. A avaliação consistiu na obtenção de história clínica com ênfase à presença de sintomas do

## THE INFLUENCE OF AGE AND PROSTATIC VOLUME ON PSA



**Figure 1** - Direct correlation between increase of Age and increase of the Prostate Volume. The majority of patients younger than 50 years presented prostate volume lower than 40g.

*Correlação direta entre o aumento da idade e o aumento do volume prostático. A maioria dos pacientes com menos de 50 anos exibiu volume prostático menor que 40g.*

trato urinário baixo, exame físico incluindo o toque retal, dosagem dos níveis séricos do PSA, dosagem da creatinina sanguínea e urinálise.

Uroculturas só eram solicitadas quando a urinálise sugeria infecção urinária. Além disso, os pacientes responderam ao escore internacional de sintomas prostáticos e foram submetidos à ultrasonografia para mensuração do volume prostático. Todos os pacientes foram avaliados por ultrasonografia transabdominal para mensuração do volume prostático com aparelho Aloka 2000, sendo a biópsia prostática realizada com o mesmo aparelho com probe de 5 MHz acoplado.

Atualmente sabemos que o termo HPB é melhor empregado quando utilizamos o critério histológico (7), o que exigiria a realização da biópsia prostática em todos os casos. No entanto, utilizaremos neste trabalho o termo HPB para aqueles pacientes que apresentam aumento prostático indicado pela ultra-sonografia e toque retal, sendo a biópsia prostática realizada somente nos casos com PSA elevado ou toque retal suspeito.

Os critérios para inclusão dos pacientes neste estudo foram: 1)- ausência de infecção do trato urinário; 2)- ausência de história prévia de cirurgia

**Table 1** - Percentage of patients with BPH, presenting normal PSA, PSA between 4 and 10 ng/ml, and PSA grater than 10 ng/ml.

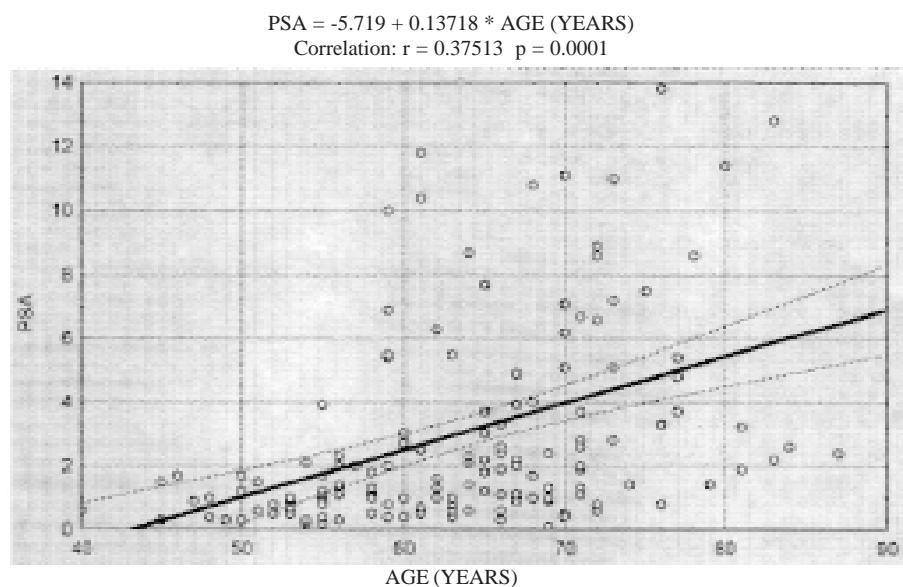
*Percentuais de pacientes portadores de hiperplasia prostática benigna com PSA normal, entre 4 e 10 ng/ml e acima de 10 ng/ml.*

PSA (ng/ml)	N Patients (%)	Elevated PSA (%)
0 – 4	125 ( 85.7)	00
4.1 – 10	14 ( 9.6)	67
> 10	7 ( 4.7)	33
	146 (100 )	100

prostática ou uretral; 3)- ausência de AcP. Foram considerados como critérios de exclusão: 1)- pacientes em uso de medicação antiandrogênica ou inibidoras da 5-α redutase e 2)- história pregressa de retenção urinária ou uso de cateter vesical de demora.

Foram utilizados anticorpos monoclonais (AXSYM® system Abbot Laboratories), onde se considera como normal variações de PSA entre 0 e 4 ng/ml. A maioria das amostras de sangue foram colhidas cerca de 3-5 dias após o toque retal realizado na primeira consulta do paciente.

## THE INFLUENCE OF AGE AND PROSTATIC VOLUME ON PSA



**Figure 2 - Correlation between PSA values and Age.**

*Correlação entre os valores do PSA e a Idade.*

**Table 2 - Correlation between the mean values of PSA, prostate volume and age.**

*Correlação entre os valores médios do PSA, volume prostático e o aumento da idade.*

Age	N	Age (mean)	PSA (mean)	Volume (mean)
40-49	8	46.00	0.8	22.86
50-59	41	55.27	1.70	40.78
60-69	56	64.80	3.15	42.27
70-91	41	75.00	4.72	54.23

Os resultados submetidos à análise estatística com um nível de significância de 5% ( $p \leq 0.05$ ). Foram efetuados os seguintes cálculos: média aritmética e desvio padrão, correlação paramétrica de Pearson, regressão linear e gráficos.

## RESULTADOS

A idade dos 146 pacientes variou de 40-91 anos ( $\text{média } 63.9 \pm 9.3$ ), sendo 132 (86%) pacientes da raça branca, 19 (12%) da raça negra e 3 (2%) pacientes de origem ou ascendência asiática.

**Table 3 - Correlation between the mean values of PSA and age and the increase in prostate volume.**

*Correlação entre os valores médios de idade e PSA e o aumento do volume prostático.*

Volume (g)	N	Volume (mean)	Age (mean)	PSA (mean)
< 30	52	21.99	60.96	1.58
30 - 39	35	34.32	63.77	2.05
40 - 49	33	47.44	65.70	3.97
≥ 60	26	97.50	68.00	6.19

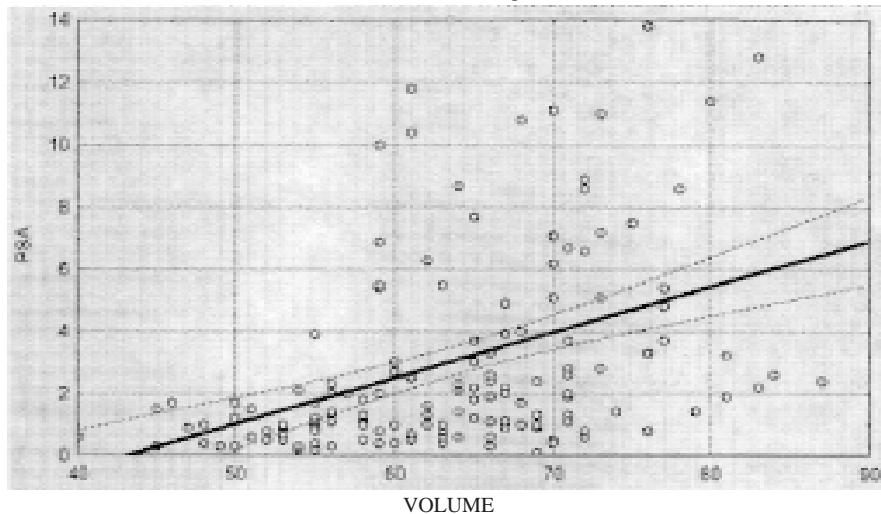
A grande maioria (85.7%) dos pacientes portadores de HPB apresentou PSA normal (Tabela-1). O PSA médio destes 146 pacientes foi 3.05 ng/ml, variando de 0.1 – 18.2 ng/ml. Cerca de 14% (21 dos 146 pacientes) apresentaram PSA elevado variando de 4.4 - 18.2 ng/m (média 9.3 ng/ml).

Em relação ao toque retal encontramos suspeita de neoplasia maligna em 18 dos 21 pacientes (85.71%), sendo 10 casos com próstatas endurecidas e 8 nódulos palpáveis.

A Tabela-1 mostra que elevações de PSA entre 4 e 10 ng/ml foram mais freqüentemente encon-

$$\text{PSA} = -0.51943 + 0.05743 * \text{VOLUME}$$

Correlation:  $r = 0.59784$   $p = 0.0001$



**Figure 3 - Correlation between PSA values and increase in Prostate Volume.**

*Correlação entre os níveis séricos do PSA e o aumento do Volume Prostático.*

tradas (67%, 14 pacientes) do que acima de 10 ng/ml (33%, 07 pacientes).

Realizamos biópsia prostática dirigida pela ultra-sonografia transretal nos 21 pacientes com PSA acima de 4 ng/ml, incluindo os 18 pacientes com toque suspeito. Os resultados foram 10 pacientes com HPB e 11 com HPB e prostatite crônica simultaneamente.

Os valores de idade, volume prostático e PSA dos 146 pacientes selecionados foram agrupados segundo 4 faixas de idade e 4 faixas de volume prostático. As médias dos valores de cada faixa são apresentados nas Tabelas-2 e 3, respectivamente.

Nas Tabelas-2 e 3 percebe-se claramente que há uma proporcionalidade direta entre as médias dos 3 parâmetros analisados (idade, volume prostático e PSA), isto é o aumento da idade é acompanhado pelos aumentos tanto dos níveis séricos do PSA quanto do volume prostático.

Foi calculada a correlação paramétrica de Pearson e a respectiva equação da reta entre os 3 parâmetros (idade x volume prostático; idade x PSA; e volume prostático x PSA) para os valores de todos os 146 pacientes simultaneamente. Todas as correlações foram estatisticamente significantes. Os coeficientes de correlação e as equações das retas são mostradas nas Figuras-1, 2 e 3.

## DISCUSSÃO

A hiperplasia prostática benigna é o tumor benigno mais freqüente do homem, com incidência progressivamente crescente com o passar da idade (4). De acordo com os dados apresentados existe claramente um aumento progressivo dos níveis sangüíneos do PSA influenciado pelo volume prostático (Tabela-3, Figura-3). Enquanto pacientes portadores de próstatas de volume inferior a 30g apresentam PSA médio de 1.5, naqueles pacientes cuja ultra-sonografia indicou próstatas superiores a 60g o PSA médio foi 6.1 ( $p = 0.0001$ ). Apesar da tendência ao aumento somente cerca de 14% dos nossos pacientes portadores de HPB confirmados patologicamente apresentou níveis séricos do PSA acima dos valores normais ( $> 4$  ng/ml). Ercole et al. (8) & Ferro et al. (9) encontraram PSA elevado em 24% e 33% dos casos confirmados de HPB, respectivamente. Brawer et al. (10) relataram elevação do PSA em 44% no pré - operatório de 81 pacientes submetidos à prostatectomia simples ou ressecção transuretral da próstata. Após a análise patológica final foram diagnosticados 11 casos de AcP, 13 PIN (Neoplasia Prostática intraepitelial), 11 prostatites agudas e somente 1 caso de HPB isolada ouacom-

panhada de PC, tendo os autores concluir que a HPB isoladamente não seria suficiente para elevar o PSA.

Estas discrepância nos valores de PSA encontradas em diferentes populações de pacientes portadores de HPB podem corresponder às diferenças na composição histológica da próstata. De acordo com Weber et al. (11) o PSA se correlaciona melhor com o peso epitelial do que com o peso prostático, podendo haver variação de até 3 vezes na contribuição epitelial ao peso prostático. Isto indica que o principal fator que influencia a elevação do PSA nos pacientes portadores de HPB é a composição histológica da mesma, principalmente o seu conteúdo epitelial.

Além do próprio aumento prostático, um segundo aspecto a ser considerado na elevação dos níveis séricos do PSA, é a presença de prostatite. Cerca de metade (11 pacientes ou 52.3%) dos nossos pacientes com PSA elevado apresentou "indícios de inflamação prostática após a biópsia prostática dirigida". Foi demonstrado experimentalmente que após um surto agudo de prostatite o PSA pode elevar-se até 28 vezes o valor basal retornando ao normal após 28 dias (12). É importante ressaltar que elevações do PSA relacionadas à prostatite geralmente envolvem a forma aguda da doença. No entanto, Pansadoro et al. (13) encontraram elevações do PSA em pacientes com prostatites crônicas bacterianas e abacterianas (15 e 6%, respectivamente) enfatizando a importância destes quadros nas interpretações do PSA usado como marcador tumoral. Desta maneira, processos inflamatórios mesmo crônicos podem elevar os níveis séricos do PSA na ausência de câncer (14). Os motivos pelos quais o tecido prostático inflamado eleva os níveis de PSA séricos ainda não foram elucidados. No entanto, os principais eventos estudados são: aumento na produção e liberação de PSA e aumento da permeabilidade vascular associada com a inflamação (15).

As elevações do PSA podem sofrer influência da idade. De acordo com a Tabela-2 o PSA médio passou de 0.8 ng/ml em pacientes com idades entre 40 e 49 para 4.7 ng/ml naqueles com idades superiores a 70 anos ( $p = 0.0001$ ). Oesterling et al. (6) relataram em estudo populacional que os níveis sanguíneos de PSA sofrem forte influência da idade aumentando

quanto mais idoso for o indivíduo. O PSA médio de indivíduos entre 40 e 49 anos foi de 0.7 ng/ml, enquanto naqueles com mais de 70 anos o PSA médio sofreu incremento para 2.0 ng/ml.

Outros estudos conduzidos por diferentes autores também enfatizam a influência da idade sobre os níveis séricos do PSA (16,17).

Apesar do nosso estudo apresentar uma influência considerável por não envolver pacientes assintomáticos oriundos da comunidade e sim aqueles avaliados a partir de uma situação clínica, podemos demonstrar que as alterações encontradas nos níveis séricos do PSA apresentam grande similaridade com aquelas já relatadas na literatura mesmo considerando estudos populacionais. Portanto algumas discordâncias ou discrepância encontradas (Ex. o PSA médio de pacientes acima de 70 anos em estudos populacionais foi de 2 ng/ml, enquanto os nossos dados indicam PSA médio de 4.7 ng/ml) podem ser assim explicadas. Além disso, é importante que conheçamos o comportamento do PSA em pacientes sintomáticos que nos procuram para avaliação, pois somente assim podemos oferecer uma orientação mais racional.

## CONCLUSÃO

Existe uma proporcionalidade direta e estatisticamente significante entre idade, volume prostático e nível sanguíneo do PSA.

Quanto maior a idade e volume prostático, maiores serão os níveis séricos do PSA. No entanto, somente 21 dos 146 pacientes (14%) apresentaram PSA acima do valor normal, sendo 14 deles ou 9.6% na faixa entre 4 e 10 ng/ml.

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## REPEATED PROSTATE BIOPSIES IN MEN WHO PERSIST WITH CLINICAL SUSPICION OF PROSTATE CANCER

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### ABSTRACT

**Purpose:** The indications for repeating biopsy in patients with suspected prostate cancer and first negative biopsy are not defined. The aim of this study was to evaluate the prevalence of prostate cancer among men who underwent repeated biopsy, and to identify criteria that allow greater precision in subsequent biopsies indications.

**Materials and Methods:** A total of 112 patients who underwent one or more transrectal sextant biopsies from March/94 to July/99 were evaluated. The indications for repeating biopsy were one or more of the following findings: elevated PSA (4 to 9.9 ng/ml and PSA density  $\geq 0.15 \text{ ng/ml/cm}^3$ , or  $\geq 10 \text{ ng/ml}$ ), suspicious digital rectal examination or transrectal ultrasonography, suspicious or unsatisfactory previous biopsy, or the presence of prostatic intraepithelial neoplasia (PIN).

**Results:** A total of 29 (25.9% of 112) patients presented with prostate cancer on repeated biopsy. Nineteen patients (17% of 112) were diagnosed on the second biopsy, and 10 patients (41.6% of 24) on the third. All positive cases presented either with a PSA of 4 to 9.9 ng/ml and PSA density  $\geq 0.15 \text{ ng/ml/cm}^3$  or a PSA  $\geq 10 \text{ ng/ml}$ . The PSA was  $\geq 10 \text{ ng/ml}$  in 9 (90%) of 10 tumors diagnosed by the third biopsy. Prostate cancer was present in 4 (40%) of 10 patients with suspicious findings on previous biopsies and in 2 (20%) of 10 with high grade PIN.

**Conclusions:** Over 25% of men with suspected prostate cancer and a first negative biopsy are found to be positive in subsequent biopsies. At least two sets of biopsies should be carried out to exclude cancer in this group of patients. A third set is indicated in men with PSA  $\geq 10 \text{ ng/ml}$  and may not be necessary in those with PSA  $< 4 \text{ ng/ml}$  or PSA of 4.0 to 9.9 ng/ml with density  $< 0.15 \text{ ng/ml/cm}^3$ .

**Key words:** prostate; prostatic neoplasms; biopsy; prostate-specific antigen  
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### INTRODUÇÃO

A biópsia prostática trans-retal (BPTR), guiada pela ultra-sonografia trans-retal (USTR), é o melhor exame diagnóstico em indivíduos com suspeita clínica de câncer de próstata (CaP), embora ainda apresente um número razoável de falsos negativos. Mesmo quando utilizados todos os testes hoje disponíveis para o rastreamento do CaP, a positividade da BPTR varia entre 20 e 40% (1). Em outras palavras, na maioria dos pacientes não se detecta malignidade. Nestes casos, situações benignas, que se confundem com o CaP durante o rastreamento, devem ser inicialmente

investigadas. Mesmo assim, em muitos destes pacientes, a suspeita clínica do CaP não pode ser totalmente afastada, e uma nova biópsia acaba sendo indicada (2).

Como existem evidências bastante convincentes de que a neoplasia intra-epitelial da próstata (PIN) de alto grau seja uma lesão pré-maligna, estes pacientes devem ser acompanhados mais de perto, com dosagem do PSA a intervalos menores, e se necessário, com a repetição da BPTR (3).

A rebiópsia pode ainda ser indicada quando o laudo histopatológico inicial é inconclusivo. Isto ocorre quando existem áreas de atipia suspeitas, ou quando a amostra coletada é inadequada (4,5).

A persistência da suspeita clínica do CaP em pacientes com biópsia prévia negativa permanece um desafio nos dias atuais. Não se sabe ao certo quantas vezes e após quanto tempo estas biópsias devem ser repetidas. Além disso, por ser um procedimento invasivo, desconfortável, sujeito a complicações, e de alto custo, a BPTR não pode ser realizada de forma indiscriminada. Também não estão ainda totalmente definidos quais os valores preditivos para o CaP na rebiópsia dos exames utilizados no rastreamento da doença e da biópsia inicial inconclusiva ou com PIN (4,6-8).

No presente estudo, procurou-se determinar a prevalência do CaP em pacientes submetidos a rebiópsias prostáticas por permanecerem com suspeita clínica após uma biópsia inicial negativa. Da mesma forma, pretendeu-se identificar critérios para a indicação de biópsias prostáticas repetidas.

## MATERIAL E MÉTODOS

Este é um estudo retrospectivo não controlado, realizado a partir da revisão de prontuários médicos. Foram incluídos todos os pacientes, atendidos entre março de 1994 e julho de 1999, que realizaram uma ou mais rebiópsias de próstata em função da persistência da suspeita clínica de CaP após uma biópsia prévia negativa.

Foram identificados 112 pacientes, com idade média de 69.4 anos (55 – 85). Destes, 88 (78.6%), 19 (17.0%), 3 (2.6%) e 2 (1.8%) realizaram respectivamente, duas, 3, 4 e 5 biópsias prostáticas, em um total de 143 rebiópsias.

As indicações para a realização destas rebiópsias foram relacionadas tanto à suspeita clínica, através do toque retal (TR), antígeno prostático específico (PSA), e USTR, quanto ao laudo histopatológico das biópsias prévias, através da presença de PIN ou biópsia prévia inconclusiva (suspeita ou inadequada), sendo que alguns pacientes apresentavam duas ou mais indicações associadas.

Dados referentes à idade, ao TR, à USTR, à dosagem sérica do PSA e suas derivações – densidade do PSA (dPSA), velocidade do PSA (vPSA) e relação PSA livre/total (PSAl/t) – e ao diagnóstico histopatológico de cada biópsia foram coletados.

O PSA foi dosado em todos os pacientes. A fração do PSA sérico livre foi dosada em apenas 38 (33.9%) pacientes, sem que houvesse um critério padronizado para a sua indicação. Por este motivo, o índice PSAl/t foi excluído da análise dos resultados. A vPSA foi determinada somente para os pacientes com intervalo entre a biópsia inicial e final maior ou igual a 6 meses. A dPSA foi calculada para todos os pacientes com PSA entre 4 e 9.9 ng/ml, medindo-se o volume prostático através da USTR. Os pontos de corte utilizados para a análise da dPSA e vPSA foram de, respectivamente, 0.15 ng/ml/cm<sup>3</sup> e 0.75 ng/ml/ano. O PSA indicou biópsia quando entre 4 e 9.9 ng/ml e dPSA ≥ 0.15 ng/ml/cm<sup>3</sup>, ou quando ≥ 10 ng/ml independente da dPSA. A USTR indicou biópsia quando detectou área hipoeólica na zona periférica. Todos os exames ultra-sonográficos e biópsias prostáticas foram realizados de forma padronizada por um único urologista. A biópsia foi guiada pelo USTR e os fragmentos prostáticos retirados em sextante. Nas áreas consideradas suspeitas ao TR ou à USTR, ou com achado histopatológico prévio inconclusivo, indicou-se a retirada de 3 fragmentos adicionais.

O intervalo mediano entre as BPTR foi de 7.5 meses (variação 1 - 59), variando conforme a suspeita da doença e a ansiedade do paciente.

Os pacientes foram divididos em 3 grupos, de acordo com o número de biópsias realizadas (duas, 3, 4 ou mais). Estes foram analisados comparativamente em relação à porcentagem de biópsias positivas, ao intervalo entre as duas últimas biópsias, e ao número de fragmentos coletados pela última biópsia.

Os exames TR, USTR, PSA, vPSA e dPSA foram relacionados aos achados positivos ou negativos das últimas biópsias, e os valores de sensibilidade, especificidade, e valor preditivo positivo (VPP) para estes exames foram calculados. Da mesma forma, pacientes com biópsias prévias inconclusivas ou com PIN de baixo e alto graus foram avaliados quanto ao resultado das últimas biópsias.

A análise estatística foi executada no programa Epi info 6.0®. O teste t de student foi empregado para a análise das variáveis contínuas uniformemente distribuídas, o teste Mann-Whitney para variáveis contínuas não uniformemente distribuídas e o teste de qui-quadrado para comparações categóricas.

## REPEATED PROSTATE BIOPSIES

Os dados referentes a bibliografia utilizada foram armazenados em um banco de dados do programa de computador Endnote 3.0®.

### RESULTADOS

Dos 112 pacientes estudados, 29 (25.9%) apresentaram CaP (Tabela-1). A positividade para o CaP de 41.6% (10 de 24) na terceira biópsia foi estatisticamente maior que na segunda, de 17% (19 de 112) ( $p < 0.0005$ ). Nenhum caso de câncer foi detectado pela quarta ou quinta biópsia. Não houve diferença significativa com relação ao intervalo entre as duas últimas biópsias ( $p = 0.81$ ), e ao número de fragmentos coletados por biópsia ( $p = 0.50$ ) entre as segundas e terceiras biópsias. Também não houve diferença entre a média dos valores de PSA que antecederam a estas biópsia, iguais a  $13.5 \pm 10.4$  e  $14.7 \pm 8.8$  ng/ml, respectivamente ( $p = 0.52$ ).

O tempo de seguimento médio decorrido entre a primeira e última biópsia para os homens com e sem CaP na rebiópsia foi igual a  $17.2 \pm 12.6$  e  $14.6 \pm 14.4$  meses ( $p = 0.38$ ). A idade média dos pacientes

com CaP na rebiópsia foi maior que a dos pacientes sem CaP ( $71.6 \pm 5.9$  e  $68.7 \pm 6.2$  anos;  $p = 0.03$ ).

Os resultados da segunda e terceira biópsia, representados na Tabela-2, foram divididos de acordo com os valores de PSA. Pacientes com PSA  $< 4$  ng/ml não apresentaram CaP. Em 13 (68.4%) dos 19 casos positivos na segunda biópsia e em 9 (90%) dos 10 casos na terceira o PSA foi  $\geq 10$  ng/ml.

A Tabela-3 apresenta os resultados obtidos pelos exames para detecção do CaP. O PSA foi considerado alterado quando entre 4 e 9.9 ng/ml e dPSA  $\geq 0.15$  ng/ml/cm<sup>3</sup> ou quando  $\geq 10$  ng/ml. Todos os pacientes com CaP apresentaram PSA alterado, sendo que este foi o indicador mais sensível (100%). O TR foi o exame que apresentou o menor número de falso positivos, sendo o indicador isolado mais específico (80.7%). A combinação PSA + TR alterados formou o indicador com o maior valor preditivo positivo (53.3%) e a maior especificidade (91.6%), às custas de uma baixa sensibilidade (27.9%). Todos os pacientes com CaP e PSA entre 4 e 9.9 ng/ml apresentaram dPSA  $\geq 0.15$  ng/ml/cm<sup>3</sup>.

**Table 1 - Incidence of prostate cancer according to the number of biopsies.**

*Incidência de câncer de próstata segundo o número de biópsias realizadas.*

Biopsies	Patients	Cancer	Positive	Interval*	N of Fragments**
2	112	19	17.0%	$12.8 \pm 13.4$	$7.0 \pm 1.7$
3	24	10	41.6%	$9.2 \pm 18.2$	$7.9 \pm 3.7$
4 ou +	5	0	0%	$6.8 \pm 3.5$	$9.0 \pm 2.4$
Total	112	29	25.9%	$12.1 \pm 12.6$	$7.2 \pm 2.9$

\* Interval in months between the last 2 biopsies; \*\* number of fragments in the final biopsy.

\* Intervalo em meses entre as duas últimas biópsias; \*\* No. fragmentos da biópsia final.

**Table 2 - Incidence of prostate cancer according to the PSA value before the second and the third biopsy.**

*Incidência de câncer de próstata de acordo com o PSA prévio à segunda e terceira biópsias.*

PSA (ng/ml)	Second Biopsy			Third Biopsy		
	Patients	Cancer	Positive	Patients	Cancer	Positive
< 4	4 (3.6%)	0	0%	1 (4.2%)	0	0%
4 - 9.9	49 (43.8%)	6	12.2%	6 (25%)	1	16.6%
$\geq 10$	59 (52.6%)	13	22%	17 (70.8%)	9	52.9%

## REPEATED PROSTATE BIOPSIES

**Table 3 - Results of the exams for prostate cancer detection in patients submitted to re-biopsies.**

*Resultados dos exames para detecção do câncer de próstata em rebiópsias.*

Exams	Ca / total	PPV	Sensibility	Specificity
altered TRUS	12 / 46	26.1%	41.4%	59.0%
altered RE	8 / 24	33.3%	27.6%	80.7%
altered PSA*	29 / 89	32.6%	100.0%	27.7%
altered PSA + RE	8 / 15	53.3%	27.6%	91.6%
PSA $\geq 4 \leq 9.9$ ng/ml	7 / 49	14.3%	24.1%	34.4%
With PSAd $< 0.15$ ng/ml/cm <sup>3</sup>	0 / 20	-	-	-
With PSAd $\geq 0.15$ ng/ml/cm <sup>3</sup>	7 / 29	24.1%	24.1%	73.5%
PSA $\geq 10$ ng/ml	22 / 60	36.7%	75.9%	54.2%
PSAv $\geq 0.75$ ng/ml/year	13 / 35	37.1%	44.8%	73.5%

PPV = positive predictive value,

\* = PSA levels  $\geq 10$  ng/ml or PSA  $\geq 4 \leq 9.9$  ng/ml + PSAd  $\geq 0.15$  ng/ml/cm<sup>3</sup>.

PSAd = prostatic specific antigen density, PSAv = prostatic specific antigen velocity.

PPV = Valor Preditivo Positivo; \* Níveis séricos totais de PSA  $\geq 10$  ng/ml ou PSA entre 4 e 9.9 ng/ml com dPSA  $\geq 0.15$  ng/ml/cm<sup>3</sup>.

**Table 4 - Pathological results of previous and final biopsies.**

*Resultados histopatológicos das biópsias prévias e final.*

Previous Biopsy	Final Biopsy		Total	PPV
	Without Cancer	With Cancer		
Normal	49	17	66	25.7%
Low Grade PIN	5	1	06	16.6%
High Grade PIN	8	2	10	20.0%
Inadequate	15	5	20	25.0%
Suspicious	6	4	10	40.0%
Total	83	29	112	25.9%

PPV = Positive Predictive Value

PPV = Valor Preditivo Positivo

A Tabela-4 relaciona os resultados histopatológicos das biópsias prévias com da biópsia final. O CaP foi detectado em 1 (16.6%) dos 6 pacientes com PIN de baixo grau e em 2 (20%) dos 10 pacientes com PIN de alto grau. A biópsia prévia foi inadequada em 15 pacientes, dos quais 5 (25%) apresentaram CaP, e suspeita em 10 pacientes, dos quais 4 (40.0%) apresentaram resultado positivo.

## DISCUSSÃO

Ainda não existe um consenso na conduta dos pacientes com suspeita clínica de CaP após uma biópsia inicial negativa.

A biópsia guiada pelo USTR, realizada de forma aleatória, em sextante e em áreas suspeitas, caso existam, foi durante vários anos o método de escolha para o diagnóstico histopatológico. O alto índice de falsos negativos ligados a esta técnica interessou alguns pesquisadores a buscarem métodos mais eficazes que apresentassem poucas complicações. Levine et al. (9), ao realizar duas biópsias em sextante consecutivas, em uma única visita, detectaram 30% de casos adicionais. Desta forma, pode comprovar que os casos de CaP descritos por estudos de rebiópsias, como o presente, representam na verdade falso negativos. Eskew et al. (10) introdu-

ziram a biópsia prostática em 5 regiões, na qual fragmentos adicionais aos em sextante foram retirados das extremidades laterais e da porção central da glândula. Com esta nova técnica, aumentou em 35% o número de casos detectados, todos fora da área habitualmente biopsiada pela técnica em sextante, sem aumento nas complicações. Esta técnica, facilmente reproduzível, é válida sobretudo para as rebiópsias, quando a primeira biópsia em sextante foi negativa. Aplicada à primeira biópsia, talvez contribua para a diminuição do número de biópsias repetidas.

Em aproximadamente 20% dos casos, o CaP pode aparecer na zona de transição (11). A biópsia de rotina desta zona prostática é ainda um assunto controverso, principalmente nos casos em que há aumento persistente do PSA não explicado por biópsia prévia, possivelmente relacionado a tumores localizados nesta região (12).

No presente estudo, apenas a zona periférica foi biopsiada, pelo método em sextante, com fragmentos adicionais em áreas suspeitas.

Em diversos estudos, a prevalência geral do CaP nas rebiópsias variou entre 20 e 40% (2,5,6,13-15). Já os índices de positividade da terceira biópsia, quando analisada isoladamente, variaram entre 8 e 26% (2,5,13). Keeth et al. (2) realizaram um estudo no qual 1136 pacientes submeteram-se a uma ou mais biópsias prostáticas por apresentarem PSA entre 4 e 9.9 ng/ml, caso TR e/ou USTR estivessem alterados, ou PSA  $\geq 10$  ng/ml, independente de outros achados. Estes pacientes, parte de um estudo longitudinal de screening do CaP, foram desta forma rebiopsiados sistematicamente a cada 6 meses. Enquanto 34% apresentaram CaP já na primeira biópsia, 427 (37.6%) pacientes foram rebiopsiados. Destes, 82 de 427 (19%) tinham CaP na segunda biópsia, 16 de 203 (8%) na terceira e 6 de 91 (7%) após quatro ou mais biópsias, resultando em um índice de positividade geral das rebiópsias de 24.4%. Este autor conclui que pacientes que mantêm suspeita clínica de CaP deveriam realizar pelo menos duas biópsias prostáticas, e que uma terceira biópsia deve ser considerada para os pacientes com PSA  $\geq 10$  ng/ml ou TR alterado.

O Serviço onde o presente estudo foi desenvolvido apresenta um índice de positividade de 39% en-

tre as biópsias iniciais (16). A prevalência geral de CaP em pacientes submetidos à rebiópsias prostáticas por permanecerem com suspeita clínica da doença foi de 25.9% (29 de 112). A positividade na segunda biópsia foi de 17% (19 de 112) e na terceira foi de 41.6% (10 de 24). Este último índice é superior aos de outros estudos da literatura, sendo possível verificar que houve uma seleção de pacientes com alta suspeita clínica entre os que se submeteram à terceira biópsia. De fato, a proporção de pacientes com PSA  $\geq 10$  ng/ml que foram à segunda biópsia (52.7%) foi menor do que a taxa dos que foram à terceira (70.8%). Dentre estes últimos, encontraram-se 9 (90%) dos 10 tumores detectados na terceira biópsia. Estes resultados confirmam que pacientes que permanecem com suspeita clínica de CaP após uma biópsia inicial negativa devem realizar pelo menos duas biópsias prostáticas, e que uma terceira biópsia deve ser considerada principalmente no grupo de pacientes com PSA  $\geq 10$  ng/ml. Vários autores concordam que, na presença de suspeita clínica mantida, pelo menos uma rebiópsia deve ser realizada (5,6,13,14).

Apenas 5 (4.5%) dos 112 pacientes submeteram-se a 4 ou mais rebiópsias, todos por PSA alterado, sendo que em nenhum deste foi encontrada doença maligna. Este dado sugere que após três biópsias negativas, a chance de detecção de CaP diminui, embora o número baixo de pacientes não permita uma conclusão definitiva.

Vários estudos visando reduzir o número de biópsias prostáticas repetidas foram realizados nos últimos anos, envolvendo o TR e o PSA e suas derivadas. Fleshner et al. (6) definiram um subgrupo entre pacientes rebiopsiados que consideraram ser o de mais baixo risco para o CaP, por apresentarem as seguintes características: PSA  $< 10$  ng/ml, dPSA  $< 0.15$  ng/ml/cm<sup>3</sup>, vPSA  $< 0.75$  ng/ml/ano, ausência de PIN ou atipia em biópsia prévia, USG e TR negativos e ausência de história familiar. Entre 21 pacientes, 5 (23.8%) apresentaram CaP em uma biópsia subsequente. Estes dados sugerem que, através dos exames disponíveis atualmente, ainda não é possível identificar um subgrupo de pacientes com baixo risco que possa ser poupar da repetição da biópsia prostática. Catalona et al. (17) realizaram BPTR em 332 homens com PSA entre 2.5 e 4 ng/ml, entre os quais obteve um índice de

positividade de 22%, demonstrando que nem os pacientes com PSA < 4 ng/ml estão livres de apresentarem a doença. Keetch et al. (8) estudando a dPSA em pacientes com biópsia prévia negativa e PSA entre 4 e 9.9 ng/ml, concluíram que uma proporção significativa de tumores deixariam de ser diagnosticados caso pacientes neste grupo e dPSA < 0.15 ng/ml/cm<sup>3</sup> fossem poupadados de biópsia. Em recente estudo realizado por Fowler et al. (15) a relação PSA livre/total (PSAl/t) apresentaram o maior valor preditivo positivo para o CaP em rebiópsias. Djavan et al. (18), com um ponto de corte de 30% para o PSAl/t, detectaram 90% dos cânceres (sensibilidade) e eliminou 50% das biópsias repetidas (especificidade).

Todos os casos positivos do presente estudo apresentavam PSA alterado (entre 4 e 9.9 ng/ml e dPSA ≥ 0.15 ng/ml/cm<sup>3</sup> ou ≥ 10 ng/ml), o que demonstra a grande sensibilidade deste índice na detecção do CaP em rebiópsias. Além disso, sugere que os 4 pacientes com PSA < 4 ng/ml e TR alterado, e os 27 com PSA entre 4 e 9.9 ng/ml e dPSA < 0.15 ng/ml/cm<sup>3</sup> poderiam ter sido poupadados da repetição da biópsia.

Entre os resultados histopatológicos do presente estudo, a biópsia prévia suspeita apresentou valor preditivo positivo de 40% (4 de 10), confirmando a estreita relação deste achado com o CaP nas rebiópsias, embora a amostra seja pequena (4,5). Em estudo recente, Iczkowski et al. (4) encontraram câncer em 42% dos pacientes com proliferação acinar pequena atípica (ASAP) em biópsias prévias. Curiosamente, não houve associação entre PIN de alto grau e o CaP nas rebiópsias analisadas. Em apenas 2 (20%) dos 10 casos com esta alteração na biópsia inicial foi encontrado CaP nas rebiópsias. Este resultado é similar ao encontrado por Fowler et al. (15), porém difere de uma série de estudos que apontam o PIN de alto grau como lesão pré-neoplásica com forte associação com o CaP (3,14).

## CONCLUSÕES

Aproximadamente 25% dos homens com suspeita clínica para o CaP e biópsia prévia negativa apresentam câncer em biópsias subsequentes. Pelo menos duas biópsias devem ser realizadas nestes pacientes. Uma terceira deve ser conduzida nos homens

com PSA ≥ 10 ng/ml, sendo desnecessária nos que apresentam PSA < 4 ng/ml ou PSA entre 4 e 9.9 ng/ml e dPSA < 0.15 ng/ml/cm<sup>3</sup>. Pacientes com biópsia prévia suspeita têm 40% de chance de portarem câncer, e devem, portanto ser rebiopsiados.

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## GLEASON SCORE. COMPARATIVE STUDY BETWEEN TRANSRECTAL PROSTATE BIOPSY AND RADICAL PROSTATECTOMY SPECIMEN

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### ABSTRACT

**Objectives:** We prospectively studied 46 patients with localized prostate cancer and compared the Gleason score of transrectal prostate biopsies to those of radical prostatectomy specimens in order to evaluate how precisely Gleason grading of prostate biopsy could predict definitive Gleason score of radical prostatectomy specimen.

**Material and Methods:** PSA and digital rectal examination were used for screening 2,815 patients for prostate cancer. Patients whose PSA were greater than 4.0 ng/ml and/or had abnormal digital rectal examination underwent transrectal prostate biopsy. The biopsy Gleason score of 46 patients operated upon in our service was compared to the Gleason score of the correspondent radical prostatectomy specimen. Wilcoxon test was used to verify if discrepancies found between biopsy and prostate cancer specimen were statistically significant.

**Results:** It was found coincidence of Gleason score in 20 patients (43.5%). Gleason score of radical prostatectomy specimen was underestimated by biopsy in 21 patients (45.6%) and overestimated in 5 patients (10.9%). It was also observed that discrepancies were higher in those cases classified by biopsy as “well differentiated cancer”.

**Conclusions:** Accuracy of histological grading (Gleason score) of prostate biopsy specimens is reasonable. Nevertheless, its limitations should be taken into account when choosing therapeutic options, particularly in cases of apparently “well differentiated cancer”.

**Key words:** prostate; prostatic neoplasm; biopsy; prostatectomy; neoplasm staging

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### INTRODUÇÃO

A graduação histológica do tecido retirado por meio da prostatectomia radical é de grande importância na definição do prognóstico do paciente (1-4). A técnica introduzida por Gleason & Mellinger ganhou aceitação mundial e é considerada padrão na graduação histológica do CaP (3). No entanto, o escore de Gleason da biópsia é freqüentemente diferente daquele observado na peça cirúrgica o que pode resultar em inadequações na avaliação da doença e do tratamento (5-7). Essas diferenças podem ser devidas à subjetividade do método de avaliação da biópsia sendo comuns resultados discrepantes quando uma biópsia é analisada por diferentes patologistas e mesmo quando um determinado patologista

analisa duas vezes seu próprio material (8). Isto pode ser particularmente importante nos casos de subestimação do grau de Gleason pela biópsia, situação na qual poderia ser indicado tratamento conservador para um tumor que se mostra bem diferenciado quando, na verdade, a doença é mais agressiva do que aparenta. O objetivo deste trabalho foi verificar a precisão da biópsia na determinação do escore de Gleason do produto da prostatectomia radical de pacientes que tiveram CaP diagnosticado em programa de rastreamento para esta doença.

### MATERIAL E MÉTODOS

De 30 de março a 3 de abril de 1998 foram convocados 3000 homens assintomáticos com idade

compreendida entre 50 e 70 anos por intermédio dos meios de comunicação de massa para rastreamento gratuito de CaP. Compareceram 2815 pacientes que foram submetidos a dosagem de PSA total e exame físico prostático (EFP). Os pacientes com PSA maior que 4,0 ng/ml, EFP anormal ou que apresentaram ambas as condições foram orientados a realizar biópsia transretal de próstata. Os pacientes com diagnóstico de adenocarcinoma de próstata foram clinicamente estadiados sendo proposta prostatectomia radical para os casos em que o estadio clínico era T1C e T2. Apenas pacientes sem tratamento prévio para CaP foram incluídos no estudo. O escore de Gleason dos fragmentos da biópsia foi comparado com o da peça cirúrgica da prostatectomia radical de 46 pacientes operados (idade variando entre 51 e 71 anos com média = 63,2) dos quais 38 (82,6%) eram da raça branca e 8 (17,4%) da raça negra. Para efeito de comparação, os tumores foram também subdivididos quanto ao escore de Gleason em grupos: 2-4; 5-6 e 7-10 sendo chamados respectivamente de bem diferenciados, moderadamente diferenciados e indiferenciados. Feito isto, verificou-se em quantas situações houve mudança de classificação do tumor quanto ao grau de diferenciação. Os resultados foram estatisticamente analisados por meio do teste de Wilcoxon.

## RESULTADOS

Foi diagnosticado CaP em 78 homens dos quais 46 foram submetidos a prostatectomia radical em nosso serviço. O escore de Gleason dos fragmen-

tos das biópsias foi comparado com o escore obtido na peça cirúrgica e os resultados podem ser vistos na Tabela-1.

Por meio da mesma comparação, verificou-se que houve subestimação pela biópsia em 21 casos (45,6%), superestimação em 5 casos (10,9%) e coincidência de grau nos 20 casos restantes (43,5%).

A comparação do grau de Gleason da biópsia e da peça cirúrgica da amostra total está apresentada na Tabela-2.

A discrepância numérica que ocorreu nos 26 casos em que não houve concordância entre biópsia e peça cirúrgica pode ser vista na Tabela-3.

Quando subdividimos os tumores diagnosticados em bem diferenciados (Gleason 2-4); moderadamente diferenciados (Gleason 5 e 6) e indiferenciados (Gleason 7-10), notamos que em 28 casos houve coincidência de classificação entre a biópsia e a peça cirúrgica, havendo 17 casos de subestimação e apenas 1 caso de hiperestimação.

**Table 2 - Comparison between Gleason score of biopsy and surgical specimen in the total sample.**

*Comparação do escore de Gleason entre biópsia e peça cirúrgica da amostra total.*

	Median	Percentile 25	Percentile 75
<b>Biopsy</b>	6	6	7
<b>Surgical</b>	7	6	7
<b>Specimen</b>			

*Wilcoxon test, p = 0,001*

**Table 1 - Correlation between Gleason score of needle biopsy and radical prostatectomy specimen.**

*Correlação entre o escore de Gleason da biópsia e da peça cirúrgica.*

<b>Gleason Score in Biopsy</b>	<b>Gleason Score in Surgical Specimen</b>						<b>Total</b>
	4	5	6	7	8	9	
4		2	1	1			4
5		1	2	2		1	6
6		2	7	10			19
7			1	11	1		13
8				2	1		3
9						1	1
<b>Total</b>	0	5	11	26	2	2	

**Table 3 - Numerical discrepancy of discordant cases between biopsy and surgical specimens.***Discrepância numérica dos casos de discordância entre biópsia e peça cirúrgica*

	<b>1 point</b>	<b>2 points</b>	<b>3 points</b>	<b>4 points</b>	<b>5 points</b>
<b>Underestimation</b>	15 ( 71,3%)	3 (14,3%)	1 (4,8%)	1 (4,8%)	1 (4,8%)
<b>Overestimation</b>	5 (100%)	-	-	-	-

## DISCUSSÃO

A graduação de Gleason da peça cirúrgica da prostatectomia radical é um importante fator prognóstico para pacientes com CaP. Quando estamos diante de uma biópsia pré-operatória diagnóstica com resultado de câncer, a decisão a ser tomada baseia-se, em parte, na desejável boa correlação entre a graduação histológica da biópsia e da peça cirúrgica. No entanto, o CaP é sabidamente uma doença multifocal o que leva à possibilidade de erros no processo de amostragem (1). De fato, o escore de Gleason da biópsia freqüentemente é diferente daquele verificado no produto da prostatectomia radical (1,5-7). Mesmo Gleason, estudando seu próprio material, notou erros de subestadiamento em até 50% das biópsias analisadas (8). A análise de nossos resultados mostra que vários problemas potenciais precisam ser levados em conta quando se usa o escore de Gleason de uma biópsia para se tomar decisões pois mudanças de grupo (bem diferenciado, moderadamente diferenciado e indiferenciado) ocorreram em 37% dos casos. Grandes discrepâncias na graduação de Gleason (diferenças iguais ou maiores que 2 pontos) foram notadas em 28,6% dos casos, sendo as diferenças de pontuação encontradas entre biópsia e peça cirúrgica estatisticamente significantes. Além disso, pudemos verificar que 100% dos tumores que se mostravam bem diferenciados (Gleason 4) na biópsia provaram ser mais indiferenciados no resultado anatomo-patológico final (Gleason 5, 6 ou 7).

O risco de conduta inadequada parece ser mais alto justamente nos tumores aparentemente bem diferenciados pois quanto mais indiferenciado se apresenta um tumor na biópsia, maior a coincidência no estadiamento patológico final, fato já de-

monstrado por Steinberg que comprovou que 64% das biópsias com grau 5-6 apresentavam coincidência com a peça cirúrgica (9). Quando se analisa o que acontece com biópsias cujo escore de Gleason é maior ou igual a 7, a coincidência na prostatectomia radical chega a 87,5%. Em nosso material, nos 17 casos classificados pela biópsia como indiferenciados, houve confirmação na peça cirúrgica em 16 casos (94,1%) e apenas 1 caso foi reclassificado como sendo de tumor moderadamente diferenciado. Conclui-se disto que os achados eventualmente preocupantes numa biópsia (escore  $\geq 7$ ) podem na realidade ter grande chance de mudarem para escala maior (8-10). Achados favoráveis na biópsia prostática não nos dão segurança de que o tumor da peça cirúrgica não possa ser mais agressivo do que aparenta ser na biópsia.

A importância da interpretação adequada dos achados da biópsia reside no fato de alguns autores sugerirem conduta expectante num tumor de escore de Gleason mais baixo e níveis menos elevados de PSA (10,11) quando talvez a melhor estratégia terapêutica nos levasse a recomendar tratamento mais agressivo.

Existem vários motivos para explicar os erros de interpretação do grau de Gleason de uma biópsia. O primeiro deles é o erro do próprio patologista especialmente no que toca a subestimação do referido grau (8,12). Steinberg et al., reanalisaram 87 biópsias com tumores classificados como Gleason 2-4 encaminhadas de outros serviços de patologia, verificando que apenas em 4 casos (4,6%) o escore se manteve em 2-4, enquanto que 68 casos (78,2%) foram classificados como escore 5-6. Em outras palavras, quando recebemos do patologista a informação de que o câncer numa biópsia tem escore 2-4, é praticamente certo que o escore real seja pelo menos 5-6 (9).

Outra fonte de discrepância entre o grau atribuído ao tumor na biópsia e na peça cirúrgica é o achado, na biópsia, de tumores com características limítrofes entre um grau e outro provocando confusão na leitura da lâmina pelo patologista e aumentando a variação inter-examinador.

Finalmente, a fonte de discrepância pode estar em erros de amostragem. Um exemplo comum deste tipo de erro ocorre quando existe uma área na próstata onde o tumor apresenta grau elevado e esta área não é atingida pela agulha de biópsia. Tipicamente isto ocorre na biópsia cujo resultado é escore 6 (3+3) e existe uma área na próstata com escore 4 o que resulta num laudo final na peça cirúrgica de 7 (3+4). O erro de amostragem reverso também pode ocorrer quando uma biópsia atinge por acaso uma pequena área onde o tumor tem escore 7 (3+4) e a peça cirúrgica revela que o tumor tem escore 6 (3+3) em 99% do volume com uma minúscula área onde o escore é 7.

A vantagem de um sistema de graduação como o de Gleason é permitir estabelecer um prognóstico. Usando a graduação de Gleason da biópsia, o PSA e o estadio clínico os urologistas são capazes de estimar o estadio patológico usando as tabelas de Partin e mesmo avaliar a probabilidade de cura após a cirurgia (13,14). A desvantagem reside nos fatores expostos acima e que podem induzir a erros na escolha da melhor alternativa terapêutica em algumas situações.

## CONCLUSÕES

A confiabilidade da graduação de Gleason nas amostras teciduais obtidas por biópsia transretal, apesar de razoável, demanda atenção para suas limitações merecendo especial cuidado os casos que se mostram bem diferenciados quando se trata de discutir opções terapêuticas. A comparação de resultados de tratamentos baseada exclusivamente em dados de biópsias também precisa ser vista com reservas.

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*Isac Castro realizou a análise estatística.  
Alexsandro G. da Silva e Fátima Jesus forneceram  
apoio em informática.*

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## BLADDER HERNIATION AS CAUSE OF ACUTE URINARY OBSTRUCTION

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### ABSTRACT

Herniation of a urological structure through the inguinal canal has been previously reported, the first case in literature was described by Chauliac in 1363. This unusual condition represents 1 to 3% of the hernias.

A 63-year-old man presented with urethral catheterization due to acute urinary retention after a cardiac surgery. The patient had a 10-year history of symptoms of nocturia, frequency, poor stream and increase in volume of scrotum. Physical examination revealed a small benign prostate and a large left inguinal hernia. The patient reported that the hernia fluctuated in size with voiding. Serum electrolytes and renal function were normal. Pelvic and scrotum ultrasound and a retrograde cystography demonstrated a small amount of bladder in the anatomical position and herniation of the remaining bladder through the inguinal canal into the scrotum. The inguinal hernia was repaired and a partial cystectomy was performed. The outcome was uneventful and the patient was discharged on postoperative day 3 with urethral catheter. The catheter was maintained for 10 days and after it withdraws spontaneously diuresis was achieved. One month postoperatively the patient had high residual volume confirmed by ultrasound and a program of intermittent catheterism was necessary.

**Key words:** bladder; urinary obstruction; hernia

**Braz J Urol, 26: 614-616, 2000**

### INTRODUÇÃO

A hérnia vesical pelo canal inguinal é considerada situação clínica pouco comum, e foi descrita pela primeira vez em 1363 por Chauliac (1). Esta rara condição clínica corresponde a 1 a 3% das hérnias e apresenta quadro clínico variado, desde ausência de sintomas até retenção urinária aguda e insuficiência renal aguda (2). Descrevemos um caso clínico com breve revisão sobre o assunto.

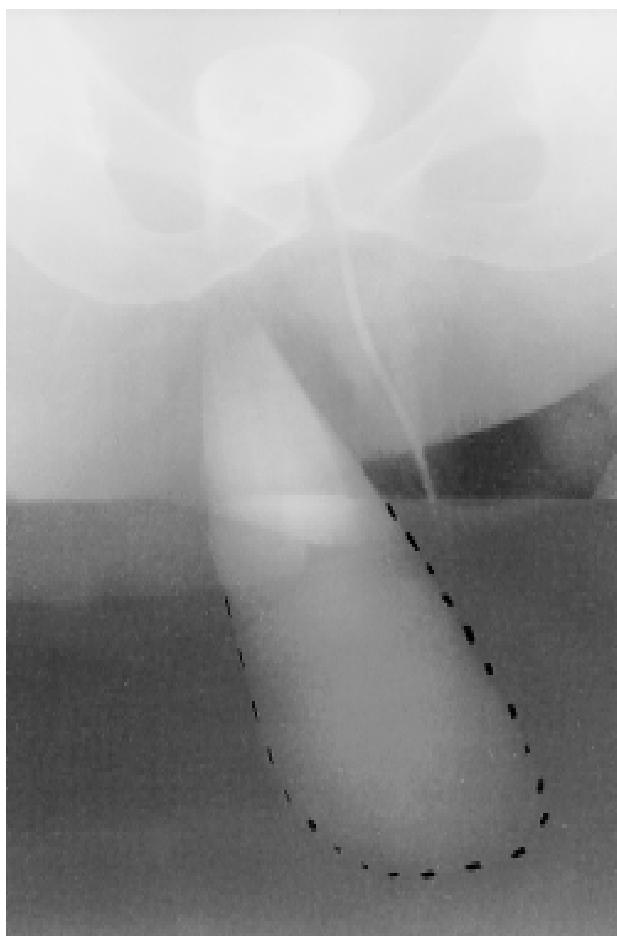
### RELATO DO CASO

Paciente W.C.A., sexo masculino, 63 anos, apresentava-se com sonda vesical de demora há 6 meses por retenção urinária aguda após cirurgia cardíaca, desde então em uso de antibioticoprotetor profiláxia.

Referia aumento progressivo do volume escrotal à direita há 10 anos, evoluindo para difi-

culdade de iniciar a micção há 2 anos, acompanhado de diminuição do jato e noctúria. Refere também necessitar de manobra de compressão manual do escroto para melhorar o jato urinário. Antecedente de coronariopatia, hipertensão arterial, diabetes, tabagismo (2 maços/dia por 35 anos) e revascularização miocárdica há 6 meses. O exame físico revelou abdome flácido, em amental, presença de grande hérnia inguino-escrotal à direita encobrindo o pênis, testículo palpável à esquerda e não palpável à direita. O toque retal revelou próstata com cerca de 40 gramas, fibroelástica sem nodulações.

Os exames laboratoriais eram normais. A ultra-sonografia mostrava rins e ureteres normais, escroto direito com grande quantidade de líquido em seu interior, ausência de septações, testículo direito normal. A uretrocistografia retrograda e miccional revelou pequena porção de bexiga no interior da pelve e a maior porção da mesma localizada no interior do escroto (Figura).



**Figure** - Voiding cystourethrogram showing the great part of the bladder inside the scrotum (dashed line) and only a small portion in the suprapubic region.

Uretrocistografia miccional demonstrando pequena porção de bexiga na pelve e o restante no interior do escroto.

O paciente foi mantido sondado e submetido a procedimento cirúrgico para reparo da hérnia utilizando-se tela de Marlex®, sendo necessária a ligadura do cordão espermático e orquiectomia direita devido a aderência ao saco herniário. A bexiga encontrava-se muito dilatada sendo realizado cistectomia parcial e colocação da mesma em posição anatômica na cavidade pélvica.

O paciente evoluiu sem intercorrências recebendo alta com sondagem vesical de demora no terceiro dia pós-operatório, que foi mantida por 10 dias. No primeiro mês pós-operatório o paciente apresentava diurese espontânea com alto resíduo

urinário pós-miccional confirmado à ultra-sonografia, sendo então instituído programa de cateterismo intermitente com sucesso.

## DISCUSSÃO

As hérnias vesicais representam 1 a 3% de todas as hérnias e acometem pacientes a partir da 5a. década de vida. Sua distribuição em relação ao sexo é de 70% no sexo masculino e 30% no feminino, e quanto ao lado acometido, é 70% à direita, 10% à esquerda e 20% bilateral (1). A maioria não apresenta sintomas e, muitas vezes, consiste em achado cirúrgico durante a correção de hérnias inguinais podendo ocorrer lesão vesical durante este procedimento (4). As hérnias sintomáticas causam disúria, polaciúria, infecções urinárias de repetição, litíase e raramente hematúria terminal e retenção urinária aguda, podendo evoluir para insuficiência renal (3). Muitos casos apresentam associação com hiperplasia prostática que pode agravar o quadro clínico, às vezes necessitando de desobstrução concomitante ao procedimento de reparo da hérnia (4).

As hérnias vesicais distribuem-se em inguinais (60%) e o restante em obturatórias, crurais, isquiáticas e da linha de Spiegel (1). As formas mais comuns de hérnia são (em ordem de freqüência): bexiga + saco peritoneal, bexiga + ureter e bexiga herniando intraperitonealmente (1).

O diagnóstico radiológico consiste na uretrocistografia retrograda e miccional e urografia excretora para localização dos ureteres. A ultra-sonografia auxilia o diagnóstico, porém a similaridade com quadros de hidrocele pode dificultar a conclusão diagnóstica.

O tratamento consiste em cirurgias para reforço da parede abdominal e reposicionamento anatômico da bexiga na cavidade pélvica.

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## POSTERIOR URETHRAL VALVE IN ADULT

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### ABSTRACT

**Objective:** To report a case of posterior urethral valve in an adult who presented with lower urinary tract symptoms and a bladder calculus.

**Case Report:** A 32 year-old man with lower urinary tract symptoms for 2 years. Retrograde urethrography revealed a normal urethra without evidence of stricture. A voiding cystourethrogram demonstrated a characteristic image of a type 1 posterior urethral valve and a 1-cm bladder stone. Valve fulguration was performed. The patient's symptoms subsided and at 14 months of follow-up, he remained asymptomatic.

**Comments:** Posterior urethral valves can be a cause of lower urinary tract symptoms in adults. A careful evaluation should be performed before the diagnosis of prostatitis is made.

**Key words:** urethra; urethral valve; adult; urinary obstruction

**Braz J Urol, 26: 617-618, 2000**

### INTRODUÇÃO

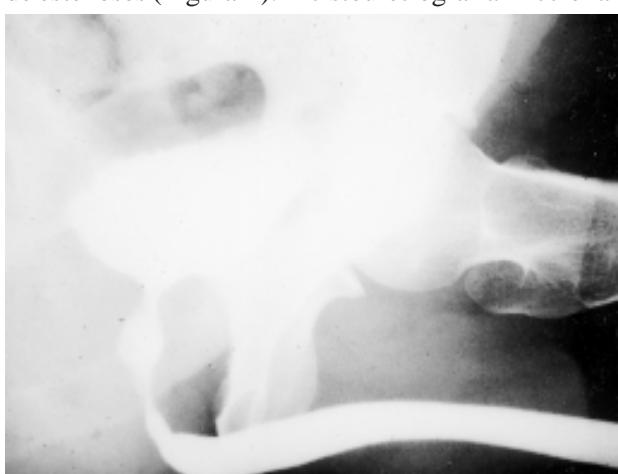
Válvulas de uretra posterior (VUP) são uma causa comum de obstrução infravesical em crianças, com a maioria dos casos apresentando-se no primeiro ano de vida. A ocorrência após a puberdade da VUP é rara, e em uma recente revisão da literatura somente haviam sido publicados 71 casos (1). Tipicamente, sintomas do trato urinário inferior em homens adultos jovens são usualmente relacionados à infecção do trato urinário, cálculos, lesões uretrais, doença neurológica ou uso de drogas que pioram a função vesical. Desde que a apresentação da VUP é rara na fase adulta, esta enfermidade comumente não entra no diagnóstico diferencial destes pacientes. Se não reconhecida prontamente, a VUP pode levar a danos intensos do trato urinário superior a depender do grau e duração da obstrução (2). Relatamos neste artigo um caso de válvula de uretra posterior em um adulto que se apresentou com sintomas do trato urinário inferior e cálculo vesical.

### RELATO DO CASO

Um homem de 32 anos apresentou-se com sintomas de polaciúria, urgência miccional, noctúria, he-

sitação e jato urinário fraco há 2 anos. Durante este período ele desenvolveu infecções urinárias severas que foram tratadas efetivamente com antibioticoterapia.

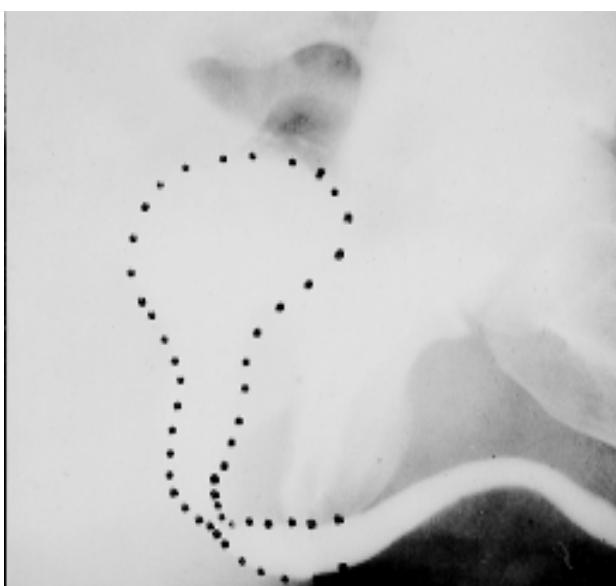
A ultra-sonografia abdominal não mostrou dilatação do trato urinário superior. A uretrogramia retrógrada revelou uma uretra normal sem evidência de estenoses (Figura-1). A cistouretrografia miccional



**Figure 1** - Retrograde urethrography demonstrating a normal urethra.

*Uretrografia retrógrada revelando uma uretra normal.*

demonstrou um cálculo vesical de 1 cm, uma bexiga trabeculada com divertículos pequenos e uma uretra posterior dilatada. A imagem foi típica de VUP a nível do verumontanum (Figura-2). O resíduo pós-miccional foi pequeno e não se detectou refluxo vesicoureteral. O exame endoscópico confirmou o diagnóstico de uma VUP tipo I, que foi fulgurada. Os sintomas do paciente resolveram-se, estando este assintomático em 14 meses de seguimento.



**Figure 2 - Cystogram demonstrating a dilated prostatic urethra and a valve at the verumontanum level.**

*Cistouretrografia miccional demonstrando a uretra prostática dilatada, e uma válvula a nível do verumontanum.*

## DISCUSSÃO

Urologistas não familiarizados com o tratamento da VUP podem encontrar dificuldades em diagnosticá-la. Mueller & Marshall reportaram 2 adultos com insuficiência renal terminal secundária a VUP. Ambos os pacientes foram diagnosticados somente após o transplante renal (2). Em ambos os casos a uretra não foi opacificada durante a cistouretrografia miccional porque não foi possível obtenção de uma fase miccional.

Adultos com VUP usualmente se apresentam com sintomas obstrutivos e irritativos, dor perineal, ardência uretral após o intercurso sexual ou ejaculação retrógrada (2,3). Alguns pacientes contudo, descrevem

um passado de sintomas urinários na infância. Nestes casos a doença não ocorre necessariamente em um estágio mais avançado. Apesar de ter apresentado sintomas por 2 anos, o trato urinário superior do nosso paciente estava normal. A razão para o aparecimento destes sintomas na fase adulta não está clara.

Ocasionalmente a VUP pode ser detectada por ultra-sonografia. Entretanto, mais comumente ela é diagnosticada por cistouretrografia miccional ou por avaliação endoscópica (2,3). Os achados nestes estudos são similares aos encontrados em crianças.

Os sintomas de VUP podem ser confundidos aos de prostatite. Isto pode levar ao uso desnecessário de antibióticos ou de outras formas de terapias, retardando o verdadeiro diagnóstico. Uma avaliação cuidadosa deveria ser realizada antes do diagnóstico de prostatite ser estabelecido. Como relatado por alguns autores pode haver dificuldades em diagnosticar VUP radiograficamente em adultos (2). Quando a suspeita clínica existe e a uretra não é visibilizada adequadamente pela cistouretrografia miccional, a urerocistoscopia é necessária. O tratamento é o mesmo daquele utilizado em crianças através de eletrocauterização endoscópica e a melhora dos sintomas obstrutivos e irritativos é esperada.

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## PENILE INVERSION AFTER BLUNT TRAUMA

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### ABSTRACT

The authors describe a rare case of external genital trauma in a young man caused by blunt mechanism. A 42 years old man was admitted on the emergency room with a blunt abdominal trauma, with lower abdominal pain and hematuria. The external genital examination revealed total absence of the penis, with the prepucial skin intact. A complete amputation of the penis was suspected. After initial resuscitation, the patient presented hipogastric expand and pain. A surgical exploration was performed and the penis was in the subcutaneous space. The penis was mobilized back to the genital region, a circumcision was performed and a visceral exploration reveals no other associated lesions. The testicles presented normal appearance. The patient was discharged on postoperative day 30, because of orthopedic associated lesions, and there was no urinary disorders or erectile disjunction until the follow up was lost.

**Key words:** penis; penile; trauma; genital

**Braz J Urol, 26: 619-620, 2000**

### INTRODUÇÃO

O traumatismo de genitália externa é patologia bastante comum, porém grandes lesões são raras. Perda de segmentos de pele, ruptura peniana ou testicular e amputações são exemplos de traumatismos de genitália externa. As causas etiológicas dividem-se em penetrantes (45%), contusas (45%) e queimaduras e acidentes industriais (10%) (1). Os autores apresentam um caso de traumatismo contuso de genitália externa de apresentação bastante rara e discutem seu tratamento.

### RELATO DO CASO

Paciente de 42 anos, do sexo masculino, foi admitido com quadro de contusão abdominal devido a acidente automobilístico há aproximadamente 20 minutos, e apresentando grande escoriação em região hipogástrica e na perna direita. Ao exame encontrava-se normotensão, taquicárdico, lúcido e o abdome apresentava-se doloroso, porém sem irritação peritoneal. O paciente encontrava-se hemodinamicamente

estável e foi encaminhado ao setor de radiologia onde foi realizado raio-x de pelve e perna direita que revelaram fratura de ramo inferior do ísquio direito e fratura de tibia direita. Durante o período de observação o paciente apresentou micção espontânea (2 episódios), queixando-se de hematúria. Ao exame genital apresentava sangramento pelo prepúcio, que ao ser reduzido demonstrou ausência completa do pênis. Foi decidido por exploração cirúrgica, pois o paciente evoluiu com abaumento da região hipogástrica, intenso quadro doloroso abdominal e apresentava suspeita de amputação traumática do pênis.

Realizada laparotomia exploradora, com abertura da pele e tecido subcutâneo, evidenciou-se o pênis em completa eversão na região hipogástrica com grande quantidade de urina infiltrando o subcutâneo (Figura). Realizou-se mobilização do pênis com reposicionamento do mesmo na região genital e postectomia. Não havia lesão uretral concomitante, bem como os corpos cavernosos encontravam-se integros. A exploração abdominal não revelou lesões intra-abdominais associadas e os testículos encontravam-se sem sinais de traumatismo. O paciente evo-



**Figure** - Surgical view of the suprapubic region demonstrating the total inversion of the penis (arrow).

Aspecto da região hipogástrica durante a exploração cirúrgica, evidenciando-se o pênis em total eversão (seta).

luiu bem, permanecendo com sonda vesical até o 4º dia pós operatório, quando ocorreu regressão do edema prepucial. A lesão tibial foi estabilizada e submetida à correção cirúrgica posteriormente, tendo o paciente alta no 30º dia pós operatório. O paciente foi seguido por 3 meses no pós operatório, sem queixas urinárias ou de disfunção sexual, período após o qual perdeu-se o seguimento.

## DISCUSSÃO

Amputações penianas parciais ou totais são casos complexos de difícil manejo e geralmente requerem o uso de microcirurgia para reimplantar peniano (2). Eversão peniana é bastante raro.

O caso apresentado destaca-se por revelar uma apresentação rara de traumatismo contuso de genitália externa. A dificuldade de diagnóstico pré-operatório envolveu uma história confusa e o exame sugestivo de amputação peniana traumática. Os princípios da reconstrução visam um resultado cosmético aceitável que permita ereções normais e não interfira com a micção e a ejaculação. Grandes perdas de tecidos necessitam rotação de retalhos cutâneos do períneo, das coxas, do escroto, enxertos livres de pele ou de malha sintética. Felizmente o caso apresentado foi de simples resolução.

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## HYPOSPADIAS. ANATOMY, EMBRYOLOGY, AND RECONSTRUCTIVE TECHNIQUES

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### ABSTRACT

Hypospadias is one of the most common congenital anomalies that can be treated with surgical reconstruction. The etiology in the majority of cases of hypospadias remains elusive. Androgens are clearly critical for penile development; however, defects in androgen metabolism and/or the androgen receptor explain only a small subset of patients with hypospadias. This paper reviews the present strategies to understanding the etiology of hypospadias. This is followed by a review of the anatomy of the male and female genitalia with an emphasis on reconstructive implications. Finally, current techniques for hypospadias repair are reviewed.

**Key words:** hypospadias; anatomy; embryology; surgical technique; congenital anomalies

**Braz J Urol, 26: 621-629, 2000**

### INTRODUCTION

Hypospadias is one of the most common congenital anomalies occurring in approximately 1:250 to 1:300 live births. In patients with severe hypospadias the genitalia may look ambiguous at birth resulting in emotional and psychological stress for parents in that the gender assignment of their baby immediately comes into question. Left-uncorrected patients with hypospadias may need to sit down to void and tend to shun intimate relationships because of the fears related to normal sexuality.

### INCIDENCE

In Europe the prevalence of hypospadias in the 1970's and 1980's has been increasing with no obvious explanation. In the United States data from two birth defects surveillance systems has also shown an unexplained doubling in the incidence of hypospadias (1). The U.S. study from the Center of Disease Control is particularly intriguing in that the incidence of severe hypospadias, not just mild forms, is increasing implying that the increase in hypospadias is not secondary to an increase in surveillance or reporting.

### ETIOLOGY

#### Androgen Metabolism

Normal sexual differentiation is dependent on testosterone and its metabolites along with the presence of a functional androgen receptor. Genetic defects in the androgen metabolism pathway (i.e. 5-alfa-II reductase defects or androgen receptor defects) are known to result in hypospadias. Although abnormalities in androgen metabolism can result in severe hypospadias this does not explain the etiology of moderate and mild forms of hypospadias (2-5).

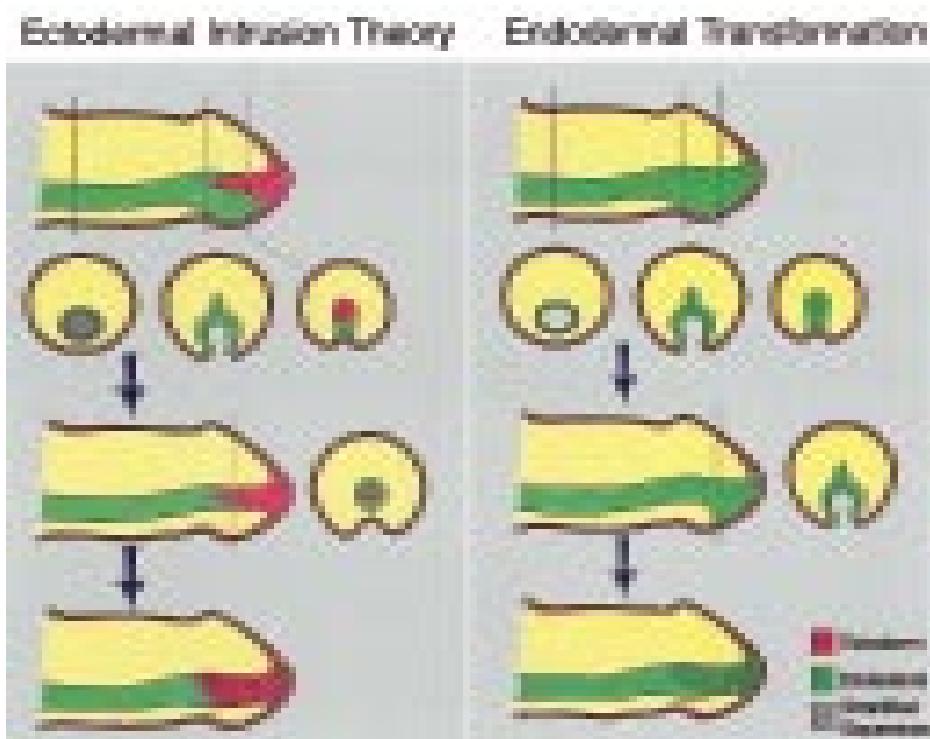
#### Abnormal Cellular Signaling

We propose an alternative hypothesis whereby hypospadias occurs by abnormal cellular signaling between tissues of the phallus during development. This hypothesis has been pursued by first defining the ontogeny of epithelial and smooth muscle differentiation markers in the developing male and female genitalia (6). The original work has been extended to anatomical studies of hypospadias and the anatomy of the clitoris (see below). Specifically, emphasis has been given to reconstructive strategies

for penile curvature and feminizing genitoplasty surgery based on the anatomical studies (7,8).

We have also focused on penile growth and differentiation. A number of important questions concerning penile growth remain unanswered. For example, the testosterone pathway and specifically DHT are critical for penile growth and differentiation. However, what about other non-androgen independent growth factors such as the insulin growth factor family. A model to study human penile growth has been designed to begin to answer some of these questions (9).

of male urethral development proposes that the urethral plate is elevated by urethral folds, which fuse ventrally in a proximal to distal sequence. Unlike its proximal counterpart, the urethra, which forms within the glans, is lined by a stratified squamous epithelium and has a more controversial development. One theory supports the idea that fusion of the urethral folds extends all the way to the tip of the glans. Another theory suggests that a solid ectodermal ingrowth of epidermis canalizes the glandular urethra. With newer immunohistochemical techniques and tissue separation and recombination experiments we pro-



**Figure 1 - Theories of human penile urethral development.** The ectodermal ingrowth theory as described in most textbooks of embryology postulates that the glandular urethra is formed by ingrowth of epidermis. Our data support the formation of the entire urethra via endodermal differentiation alone (with permission, from ref. 10).

To test the hypothesis that epithelia-mesenchymal interactions are critical for normal penile growth and differentiation an extensive study was performed using the mouse genital tubercle (10). Various epithelial-mesenchymal separation experiments were performed to show the importance of epithelial-mesenchymal signaling. When normal signaling was present the growth of the genital tubercle exhib-

ited normal growth and differentiation (defined by the presence of cartilage). In contrast, removal of the developing epithelium [epidermis (skin) and endoderm (urethra)] greatly stunted the growth of the genital tubercle.

Basic work on penile growth has led us to reexamine the embryology of the urethral development (11). The most widely accepted mechanism

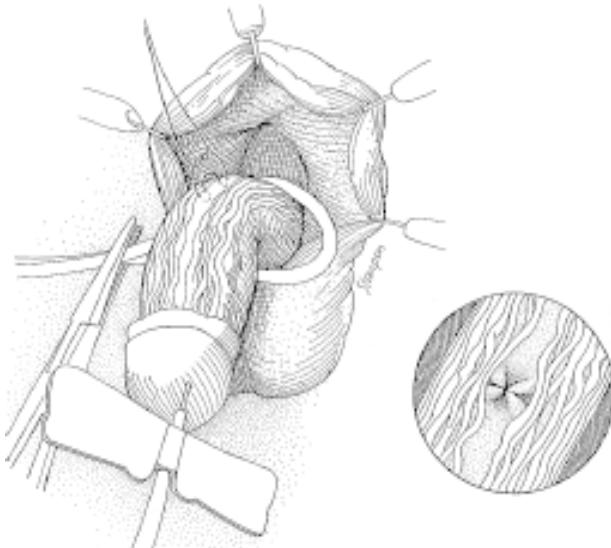
posed a new theory to explain the formation of the male distal urethra. Thirty-six human fetal phallic specimens, gestational ages 5-22 weeks, were sectioned and stained immunohistochemically with antibodies raised against different cytokeratins. Evaluation of the sections showed that the urethral plate, an extension of the urogenital sinus, extended to the tip of the phallus and maintained patency and continuity throughout the process of urethral development. The entire urethra, including the glans portion, was formed by dorsal extension and disintegration of the urethral plate combined with ventral growth and fusion of the urethral folds. Sections of the distal glandular urethra showed no evidence of a solid ectodermal ingrowth. Rather, immunostaining results at different ages suggested differentiation of the endodermal urethral plate into a stratified squamous epithelium (11). To determine whether urothelium could be induced to express a stratified squamous phenotype, mouse fetal bladder epithelium was combined with rat fetal genital tubercle mesenchyme and grown under the kidney capsule of athymic mice. The bladder epithelium differentiated into a stratified squamous epithelium. Thus, proper mesenchymal signaling may induce differentiation of urothelium into a stratified squamous epithelium, such as during development of the urethra of the glans penis. Figure-1 is a schematic of the classic theory of ectodermal intrusion contrasted with the new theory of endodermal differentiation supported by our experiments. If we are going to understand the etiology of hypospadias it is critical that we understand normal penile and urethral development.

### Endocrine Disruptors

One possible explanation for the worldwide increase in the incidence of hypospadias may be environmental contamination, which could interfere with the normal androgen pathways and normal cellular signaling. In this regard it is well established that humans continually ingest substances with known estrogenic activity such as insecticides utilized in crop production, natural plant estrogens, by-products of plastic production and pharmaceuticals. Indeed, the metal cans used in the food industry are coated inter-

nally with plastic known to contain estrogenic substances. Many of these estrogenic substances find their way ultimately into fresh and seawater in trace amounts, but are bio-accumulated and concentrated in higher organisms of the food chain. For this reason predators at the top of the food chain (large fish, birds, sea mammals and humans) accumulate high levels of estrogenic environmental contaminants. For many species of wild life the consequences for reproduction and health are devastating. For example, the thinning of eggshells in a variety of birds was ultimately traced to the estrogenic activity of insecticides to which the birds were exposed through their diet. Thus, humans and wild animals are constantly exposed to estrogenic compounds known for their ability to disrupt reproduction, so called endocrine disrupters.

Estrogenic contaminants are known to impair penile development in the American alligator (12). Moreover, the potent estrogen, estradiol 17-beta, is known to disrupt penile development in mice even through very little is known about the molecular mechanisms whereby exogenous estrogens perturb penile development (13). In a general sense the normal process of penile development is poorly understood at the cellular and molecular levels. Thus, it is



**Figure 2 - Penile curvature correction plication suture technique at the 12:00 o'clock position for the correction of ventral curvature. This technique has the theoretical advantage in that it does not injure any nerves or vessels and the sutures are placed in the thickest and hence strongest part of the tunica.**

paramount to initiate basic research into the mechanism of normal penile development in concert with studies designed to test the hypothesis that estrogenic compounds can perturb penile development. If it can be established that estrogenic endocrine disrupters are responsible for the increased incidence of hypospadias, preventive steps can be taken to minimize contact with such agents. In the final analysis prevention is the best strategy for this serious medical problem.

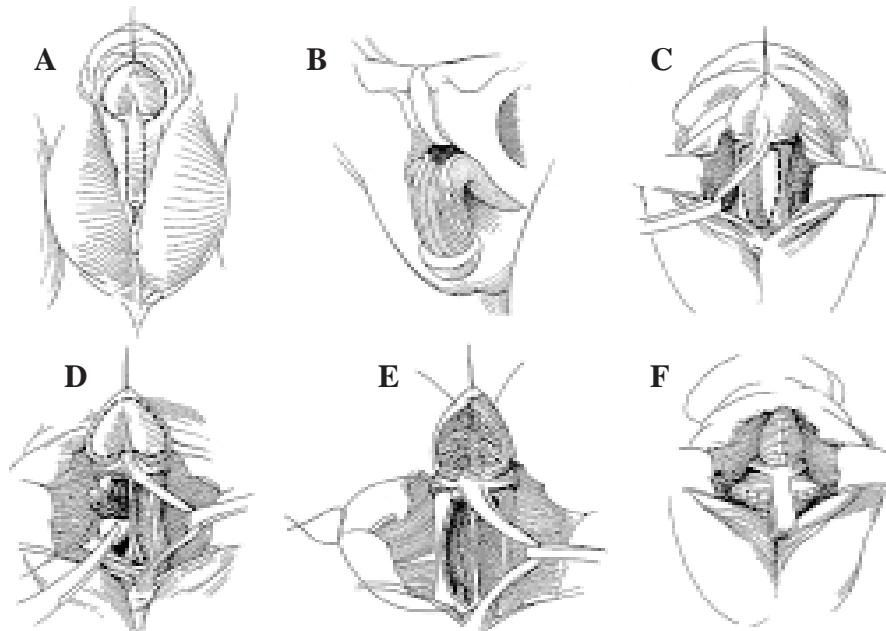
### ANATOMICAL STUDIES AND RECONSTRUCTIVE IMPLICATIONS

Over the last three years, we have performed careful anatomical studies on genital specimens between the ages of 8 and 33 weeks. In short, speci-

analysis of the male specimens revealed localization of the nerves dorsally not only at the 11 and 1 o'clock position but extending around the tunica to the junction of the corpus spongiosum and corpora cavernosa suggesting that we may be injuring these structures in penile straightening procedures (6,8).

The tunica albuginea showed consistent variations in thickness, with the mid dorsal 12 o'clock position being the thickest followed by the 5 and 7 o'clock periurethral positions. The lack of nerves and the thickness of the tunica at the 12 o'clock position have lead to the design of penile straightening procedures by the placement of plication sutures (Figure-2) (6,8).

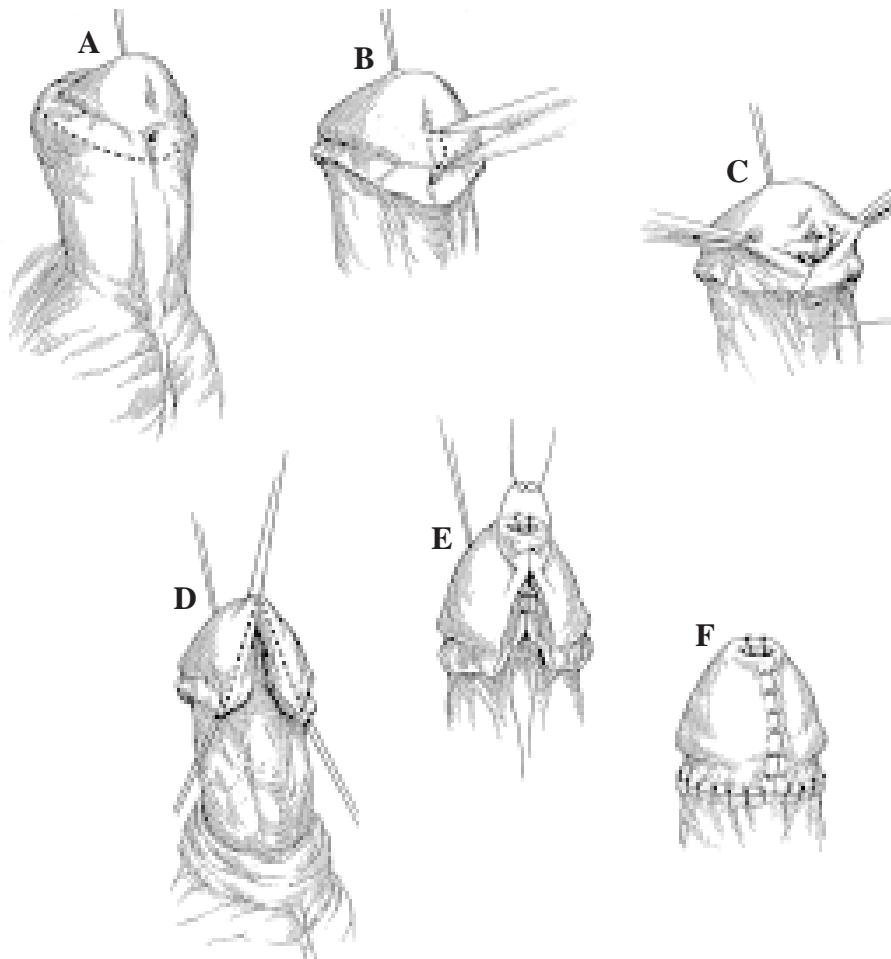
Analysis of female specimens showed that the normal fetal clitoris consists of two corporal bodies with a midline septum. The ultrastructure of the



**Figure 3 - Schematic of feminizing genitoplasty based on neuroanatomical studies.** A)- clitoroplasty incision; B)- schematic representation of nerves based on anatomical studies; C)- mobilization of urethral plate and outline for ventral incision into corporal bodies; D)- reduction of erectile tissue and incision for glans reduction; E)- corporal and glans reduction; F)- reduced glans clitoris with erectile preservation.

mens were serially sectioned and stained for epithelial, smooth muscle and nerve structures using immunocytochemical techniques. Select specimens were reconstructed in 3 dimensions to better understand the relationship between the nerves, corporal bodies and urethral spongiosum using the computer software NIH imaging and Adobe Photoshop® (6). Careful

female corporal bodies is analogous to the male counterpart. The glans clitoris forms a cap on top of the distal end of the corporal bodies. Large bundles of nerves course along the corporal bodies with the greatest density on the dorsal aspect. These anatomical relationships are useful when preserving nerves during feminizing genitoplasty surgery (Figure-3) (7).



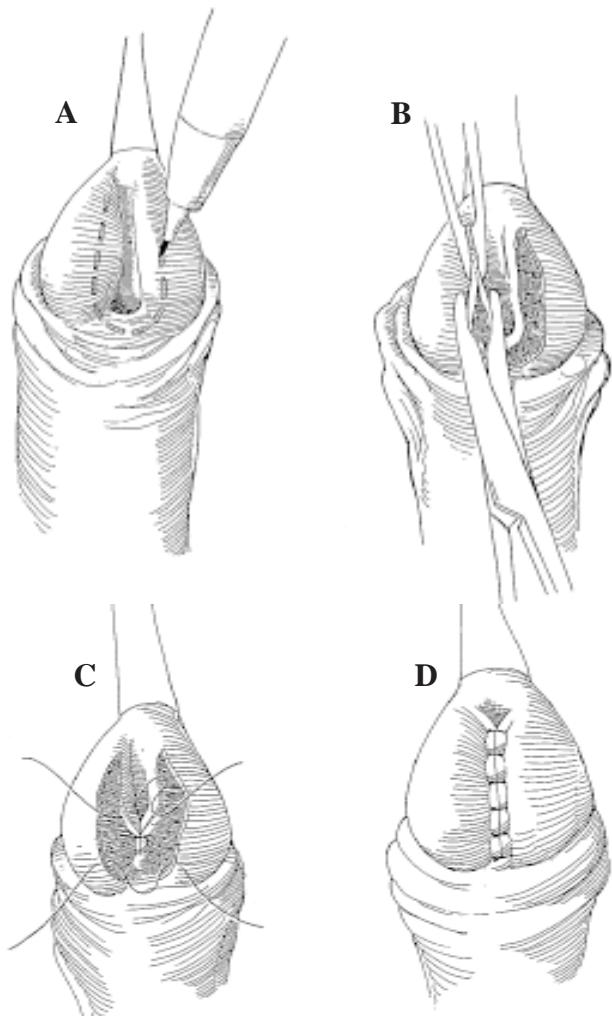
**Figure 4 - MAGPI hypospadias technique.** A)- shows the initial maneuver of the circumferential subcoronal incision; B) and C)- shows the Heineke-Mikulicz incision and closure of the dorsal meatus after excision of the dorsal web skin bridge; D)- illustrates the most critical step which is exposure of glans mesenchyme, by trimming excess skin illustrated by the dash lines in the figure, and advancing the mobile urethra with the use of a 6-0 chromic suture, or in the case of schematic a skin hook; E)- shows a two layer closure of the glans mesenchyme over the advanced urethra, allowing for a normal appearing glans with excellent support of the urethra; F)- illustrates skin closure with a sleeve approximation of the penile shaft skin. In cases where there is a ventral skin deficiency, a Byer's flap rearrangement with a standard mid-line seems appropriate. (From Hinman F Jr; *Atlas of Pediatric Urologic Surgery*. Philadelphia, WB Saunders Co, pp. 575-578, 1994, used by permission).

Finally, the ultrastructure of hypospadias has revealed that the nerves and corporal bodies have the same anatomical relationship as the normal penis. The most striking difference between the normal penis and the hypospadiac penis is the difference in vascular supply. The hypospadiac penis has huge endothelial lined vascular channels filled with red blood cells. In contrast, the normal penis has well defined small capillaries around the urethra and fanning into the glans

(8,14). The anatomy of the normal and hypospadiac penis is relevant to the surgical techniques in respect nerve and vascular preservation.

## TREATMENT

The only treatment for hypospadias is surgical repair of the anatomical defect (15-18). In experienced hands the surgery is typically performed



**Figure 5 - GAP Hypospadias technique.** A)- illustrates the initial incision; B)- shows the exposure of the glans mesenchyme by de-epithelialization of tissue, which is critical for a two-layer glans closure, allowing for good support of the urethroplasty; C)- tubularization of the neourethra followed by glans closure and (Figure D) the completed repair.

as an outpatient procedure with 80-90% of children requiring one operation. Since the surgery is elective, the optimum time as recommended by the American Academy of Pediatric Consensus Panel on genital surgery is between 6 months and 18 months (19).

### Anterior Hypospadias

The technique chosen for the repair of anterior hypospadias will depend on the anatomy of

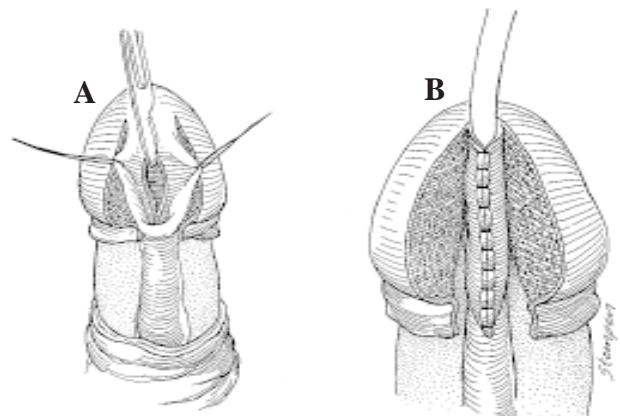
the hypospadiac penis. The most common accepted procedures are the MAGPI (meatal advancement glansplasty), the GAP (glans approximation procedure), the Mathieu or flip-flap and the tubularized incised plate urethroplasty (20-33). We have been most pleased with the results from the MAGPI and GAP procedure, which we present in more detail below. The Mathieu is based on a random flap, which is not as reliable as a vascularized pedicle graft. Long-term complications from meatal stenosis secondary to ischemia have been more common (17).

### The MAGPI Technique

The MAGPI technique was devised by Duckett in 1981 (20). This technique will provide outstanding results if appropriate patient selection is followed. The hypospadiac penis that is amenable to the MAGPI is characterized by a dorsal web of tissue within the glans that deflects the urine from either a coronal or a slightly subcoronal meatus. Once the patient is asleep, the urethra itself must have a normal ventral wall, without any thin or atretic urethral spongiosum. The urethra also must be mobile so it can be advanced into the glans (Figure-4).

### The GAP Procedure

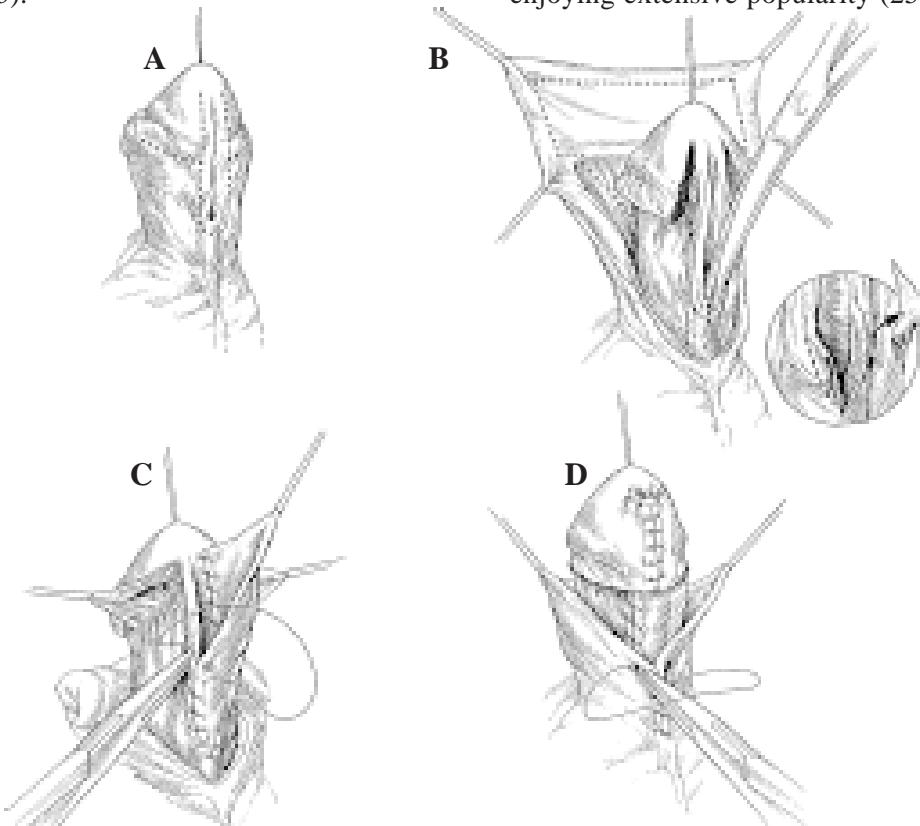
The GAP procedure is applicable in a small sub-set of patients with anterior hypospadias who



**Figure 6 - Tubularized incised plate urethroplasty.** A)- note the deep incision in the urethral plate down to corporal tissue; B)- tubularization of neourethral with subsequent glansplasty.

have a wide and deep glandular groove (21). These patients do not have a bridge of glandular tissue that typically deflects the urinary stream, as seen in patients who would be more appropriately treated with the MAGPI procedure. In the GAP procedure, the wide mouth urethra is tubularized primarily over a stent (Figure-5).

more severe hypospadias, a vascularized pedicle flap was performed. Recently the concept of the incision in the urethral plate with subsequent tubularization and secondary healing has been introduced by Snodgrass (Figure-6) (22). Short-term results have been excellent and this procedure is enjoying extensive popularity (25). One appealing



**Figure 7 - Onlay island flap hypospadias repair:** A)- a U-shaped incision is made around the urethral plate preserving a dorsal urethral strip approximately 8 mm wide; B)- shows take-down of the skin and subcutaneous tissue, as well as outlining the inner prepuce for the onlay island flap. Glans wings are mobilized along the plane of the corporal body and the glans mesenchyme; C)- show preservation of the urethral plate with penile curvature in a case of penoscrotal hypospadias; D)- illustrates suturing of the onlay flap with running 7-0 suture to the urethral plate. The flap is trimmed to obtain a 12 French caliber bougie in a child of one year of age, to prevent the complication of urethral diverticulum, which results from leaving excess tissue. The glans wings are approximated over the new urethra after maturing the meatus and then the skin is closed by a classic Byers flap skin rearrangement.

### Tubularized Incised Plate Urethroplasty

Historically, if the urethral groove was not wide enough for tubularization *in situ*, such as in the GAP or Thiersch Duplay procedure (21,24) then an alternative approach such as the Mathieu or for

aspect is the slit-like meatus, which is created with the dorsal mid-line incision. More recently, this technique has been applied to more posterior forms of hypospadias. Theoretically, there is concern about the possibility of meatal stenosis from scarring as occurs in patients with urethral stricture disease

where direct vision internal urethrotomy often leads to recurrent stricture. In hypospadias, the native virgin tissue with excellent blood supply and large vascular sinuses seems to respond to primary incision and secondary healing without scar (8,14).

### **Posterior Hypospadias**

We have been quite satisfied with the onlay island flap hypospadias technique for the majority of penile shaft and more severe cases of hypospadias (Figure-7). The onlay island flap has withstood the test of time with excellent long-term results (15,17). Preservation of the urethral plate in the onlay island flap has essentially eliminated proximal anastomotic strictures and has reduced the incidence of fistula formation. When necessary penile curvature is corrected by dorsal plication (Figure-2)(8).

Recent reports have summarized standard techniques and introduced subtle variations (26-29). Occasionally extensive surgery is necessary and in some cases multiple operations leave the unfortunate child with a suboptimal result, the patient then being classified as a "hypospadias cripple". For very severe hypospadias, the prepuce can be designed as a horseshoe style to bridge extensive gaps (30).

### **CONCLUSION**

In summary, in the last twenty years there has been an incredible evolution in the surgical treatment of hypospadias. Optical magnification, delicate tissue handling and fine sutures have greatly benefited patients and families with this congenital anomaly. The next step is to begin to understand the etiology of hypospadias. This is especially germane if the incidence of hypospadias is truly doubling. A multidisciplinary effort is warranted in the areas of androgen metabolism and epithelial-mesenchymal signaling based on the hypothesis that endocrine disrupters may account for the documented increase incidence of hypospadias. Through a better understanding of normal penile growth and urethral differentiation new strategies of prevention and treatment can be developed.

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## STROMAL MODIFICATIONS IN BENIGN PROSTATIC HYPERPLASIA AS EVIDENCED BY GLYCOSAMINOGLYCAN COMPOSITION

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### ABSTRACT

**Objective:** Benign prostatic hyperplasia (BPH) is accompanied by extensive albeit not well known modifications of the extracellular matrix. Herein the matricial composition in BPH was evaluated by analyzing the glycosaminoglycans (GAG) in the prostatic tissue.

**Material and Methods:** BPH samples were obtained from 6 patients aged 63 to 79 years who had been submitted to open prostatectomy. Controls consisted of the transitional zone of prostates from 6 young adults. GAGs were extracted by papain digestion and cetylpyridinium chloride/ethanol precipitation, assayed by a hexuronic acid method, and the concentrations were expressed as micrograms of hexuronic acid per milligram of dry, defatted tissue. Sulfated GAGs were identified and quantitated by agarose gel electrophoresis.

**Results:** The concentration of GAG in BPH ( $1.34 \pm 0.20$ ) was increased by 62% ( $p < 0.005$ ) with regard to that in the transitional zone ( $0.83 \pm 0.21$ ). The prevailing sulfated GAG both in the normal and hyperplastic prostates is dermatan sulfate. The proportions of heparan sulfate is unchanged in both cases, whereas the content of dermatan sulfate is decreased ( $49.2 \pm 6.5$  vs.  $59.9 \pm 4.1\%$ ,  $p < 0.01$ ) and that of chondroitin sulfate is increased ( $24.9 \pm 4.5$  vs.  $14.5 \pm 2.8\%$ ,  $p < 0.005$ ) in BPH samples.

**Conclusion:** GAG composition in BPH differs markedly from that of the normal transitional zone. These findings are at variance with previous reports in which less appropriate controls were used. Our results also imply that interstitial proteoglycans are more affected in BPH, which may result from cytokine-mediated stimulation of stromal cells.

**Key words:** prostate; prostatic hyperplasia; glycosaminoglycans; extracellular matrix  
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### INTRODUÇÃO

A hiperplasia prostática benigna (HPB) é acompanhada de proliferação de células epiteliais e de extensas modificações na organização do estroma. Embora diversos estudos tenham relatado dados quantitativos para esses componentes, os resultados eram de início controversos, de modo que não havia um consenso com relação a qual deles estaria aumentado (1-4). Mais recentemente, no entanto, tem se mostrado por análise morfométrica que o estroma é o componente majoritário na HPB (5). Confirmando esses achados, Walden et al. (6) mostraram que células do estroma prostático, quando comparadas com células epiteliais, expressam níveis mais bai-

xos de mRNA que codifica um inibidor da progressão do ciclo celular.

Outros estudos revelaram que alterações também ocorrem na composição do estroma. Existem evidências, por exemplo, de que a densidade de células de músculo liso está alterada no estroma hiperplásico, e que esse parâmetro pode ser usado para o acompanhamento da resposta farmacológica a medicamentos (7,8). As células de músculo liso podem também estar substituídas por fibroblastos, o que provavelmente ocorre como reação a zonas de isquemia (9).

O estroma da próstata inclui diversos componentes da matriz extracelular, como colágenos, fibras elásticas, e proteoglicanos. A identificação des-

ses últimos no tecido prostático foi feita por meio de imunohistoquímica em microscopia óptica (10,11) ou pela detecção de seqüências gênicas (6,12), e estudos recentes têm mostrado que os proteoglicanos e suas cadeias laterais de glicosaminoglicanos (GAG) desempenham um papel importante na patologia da próstata, principalmente no câncer (11,13-15).

A composição de GAG na HPB foi investigada por De Klerk (16) & Iida et al. (15), que utilizaram como controle ou a zona central ou amostras sem localização anatômica definida de próstatas normais, respectivamente. Como a grande maioria dos casos de HPB se origina na zona de transição (1), e pelo fato de que se dispõe de métodos mais seletivos para a purificação e quantificação de GAG, os resultados nos referidos trabalhos podem não refletir as alterações que ocorrem nessa doença. Essa questão foi abordada no presente trabalho, cujo objetivo foi determinar a composição de GAG em amostras de HPB, utilizando como controle a zona de transição de próstatas de adultos jovens.

## MATERIAL E MÉTODOS

As próstatas com hiperplasia benigna foram obtidas de 6 pacientes com idade variando entre 63 e 79 anos. Esses pacientes apresentavam sintomas clínicos de HPB e foram submetidos a prostatectomia aberta. O diagnóstico histopatológico posteriormente confirmou a presença de HPB em todas as amostras. Os controles consistiram da zona de transição (17,18) de próstatas obtidas durante a necropsia de 6 adultos com idade de 18 a 30 anos e que haviam morrido de acidentes. As amostras de tecido foram fixadas em acetona logo em seguida à remoção em cirurgia ou necropsia, e, após clivagem, foram delipidadas em clorofórmio/metanol (2:1, v/v) por 24 horas e secas a 60°C.

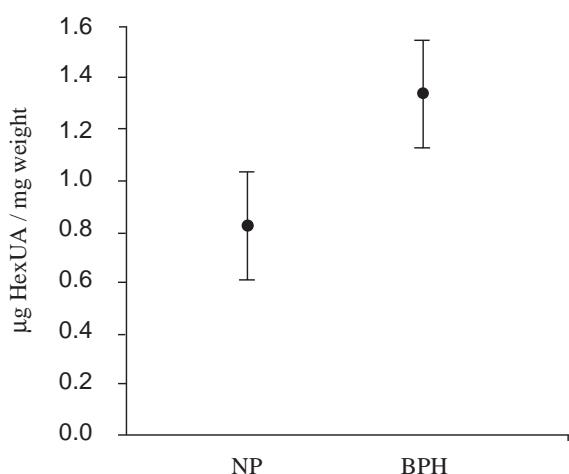
A extração e determinação da concentração tissular de GAG foi feita segundo métodos previamente descritos (19). Resumidamente, 100 a 500 mg de tecido delipidado e seco foram rehidratadas em tampão acetato de sódio 100 mM, pH 5.0, contendo cisteína 5 mM e EDTA 5 mM, por 24 horas a 4°C, e posteriormente incubadas com papaína (Sigma,

bicristalizada) nesse mesmo tampão por 24 horas a 60°C. Após centrifugação (3000xg, 20 minutos) e lavagem dos resíduos insolúveis com água, os dois sobrenadantes foram agrupados, e a esta solução adicionou-se cloreto de cetilpiridínio (Sigma) para uma concentração final de 0.5%. Essa mistura foi deixada à temperatura ambiente por 24 horas, centrifugada (3000xg, 30 minutos), e ao pellet adicionou-se NaCl 2M:etanol (100:15, v/v). Após dissolução completa do pellet, a solução foi misturada com 2 volumes de etanol absoluto e deixada a 4°C por 24 horas. Os GAGs foram então recuperados por meio de uma série de centrifugações (3000xg, 30 minutos cada) em que se lavou o pellet com etanol 80% e absoluto. O pellet final, que constitui a preparação purificada de GAG total, foi seco a 60°C, dissolvido em água, e a solução foi guardada a -20°C.

A concentração tissular de GAG total foi determinada por meio da dosagem de ácido hexurônico segundo o método do carbazol (20), utilizando-se glicuronolactona (Sigma) como padrão.

A eletroforese em gel de agarose (Dietrich and Dietrich, 1976) foi utilizada para se determinar a proporção dos diferentes tipos de GAG sulfatados. Aproximadamente 5 µg da preparação GAG total, como ácido hexurônico, foram aplicados em uma placa de gel de agarose 0.5% (Sigma) em tampão 1,3-diaminopropano 50 mM, pH 9.0. A corrida foi realizada a 80 V, e o gel foi em seguida tratado com brometo de N-Cetil-N,N,N-trimetilâmônio a 0.1% por 2 horas, e corado com azul de toluidina 0.1% em etanol absoluto:ácido acético 1% (1:1, v/v). A placa de agarose foi então digitalizada em scanner (Hewlett-Packard) e o perfil densitométrico das bandas, assim como a área dos picos, foram obtidos usando-se o programa Scion Image (Scion Corporation, USA). A identificação das bandas na placa de agarose foi feita com base na comparação com a migração de padrões de GAG comerciais (Sigma) e na susceptibilidade à degradação por GAG-liases (Cardoso et al., 1992).

Diferenças de concentração e proporção de GAG entre os grupos controle e de HPB foram analisadas pelo teste para duas amostras de Wilcoxon (21). As diferenças foram consideradas estatisticamente significativas quando  $p < 0.05$ .



**Figure** - Total glycosaminoglycans concentration in normal prostates (NP) and in benign prostatic hyperplasia (BPH). The values are expressed as the mean concentrations and the bars represent the standard deviation.

Concentração de glicosaminoglicanos totais na próstata normal (NP) e na hiperplasia prostática benigna (BPH). Os valores são a média das concentrações para cada grupo, e as barras de erro representam o desvio padrão. A diferença entre os dois grupos é significativa ( $p < 0.005$ ).

## RESULTADOS

A concentração de GAG nas amostras de próstata foi expressa em termos de microgramas de ácido hexurônico por miligrama de tecido delipidado e seco, e está mostrada na Figura. Na zona de transição de próstatas de adulto jovem essa concentração é, em média, de  $0.83 \pm 0.21 \mu\text{g}/\text{mg}$ . A mesma dosagem mostrou que, em amostras de HPB obtidas de

pacientes com idade variando entre 63 e 79 anos, a concentração de GAG é de  $1.34 \pm 0.20 \mu\text{g}/\text{mg}$ . Na HPB, portanto, a concentração de GAG está aumentada em 62% quando comparada às próstatas de adulto jovem, e essa diferença é significativa ( $p < 0.005$ ).

Os GAG sulfatados presentes nas próstatas normais e hiperplásicas, como determinado pela eletroforese em gel de agarose, são o heparan sulfato, o dermatan sulfato, e o condroitin sulfato. Tanto na zona de transição das próstatas normais quanto nas amostras de HPB, o dermatan sulfato é o GAG predominante, enquanto que o heparan sulfato está presente em proporções similares nos dois casos. Existem, no entanto, modificações significativas na HPB, com uma diminuição no conteúdo relativo do dermatan sulfato ( $p < 0.01$ ) e um aumento do condroitin sulfato ( $p < 0.005$ ) (Tabela).

## DISCUSSÃO

A purificação em “batch” de GAG por meio de resinas ou detergentes catiônicos permite a eliminação de diversos contaminantes que podem interferir na dosagem de ácido hexurônico. Os valores de concentração relatados por De Klerk (16) se baseiam em métodos menos seletivos para o isolamento de GAG, e podem portanto estar superestimados. Os nossos resultados para concentração de GAG na próstata são de fato três vezes menores, e tal diferença se manteve consistentemente em todas as amostras analisadas. Nota-se também que, pelos resultados apresentados no referido artigo, não está claro se existe modificação na concen-

**Table** - Proportions of the different sulfated glycosaminoglycans in normal prostates (NP) and in benign prostatic hyperplasia (BPH). The proportions are expressed as the percentages of the total sulfated glycosaminoglycans.

Proporção dos diferentes glicosaminoglicanos sulfatados em próstatas normais e com hiperplasia benigna (HPB). As proporções estão expressas como porcentagens de glicosaminoglicanos sulfatados totais.

Prostate	N	HS	DS	CS
Normal	6	$25.6 \pm 3.58$	$59.9 \pm 4.102$	$14.5 \pm 2.77$
BPH	6	$25.8 \pm 4.09$	$49.2 \pm 6.58^*$	$25.0 \pm 4.52^{**}$

HS = heparan sulfate, DS = dermatan sulfate, CS = condroitin sulfate. The asterisks indicate the statistical significant differences. \* =  $p < 0.01$ , \*\* =  $p < 0.005$ . N = number of prostates.

HS = heparan sulfate, DS = dermatan sulfate, CS = condroitin sulfate. As diferenças significativas em relação aos glicosaminoglicanos correspondentes das próstatas normais estão indicadas com um asterisco ( $p < 0.01$ ) ou dois (p < 0.005) asteriscos. N, número de próstatas.

tração de GAG na HPB, pois além de não se comparar a mesma região da glândula, a zona de transição não foi utilizada como controle. Sabe-se que nessa área origina-se a maior parte dos casos de HPB (1). Iida et al. (15) isolaram os GAG com método semelhante ao de De Klerk (16), e os controles consistiram de amostras de tecido prostático sem localização anatômica definida. Os resultados desse primeiro trabalho, obtidos a partir de um número pequeno de amostras e expressos em relação a peso úmido, não indicaram diferenças significativas entre HPB e os controles.

Os nossos resultados mostraram que, apesar da grande quantidade de estroma presente na zona de transição da próstata normal (18), a concentração de GAG nessa região é comparativamente baixa. Em artérias, por exemplo, essa concentração é em torno de cinco vezes maior (19). Nossos resultados também revelaram que há um aumento considerável e significativo na concentração de GAG na HPB quando comparado com as amostras de zona de transição. Além disso, os GAG de distribuição eminentemente intersticial, como o dermatam sulfato e o condroitim sulfato, apresentaram modificações de concentração relativa na HPB. Já o heparan sulfato, que está associado principalmente à membrana basal e à superfície celular (Iozzo, 1998), permaneceu inalterado. Esses dados indicam que as alterações de síntese de proteoglicanas ocorrem basicamente no estroma, onde haveria um remodelamento marcante na matriz extracelular, com consequências importantes para o metabolismo das células epiteliais e mesenquimais. É preciso notar, entretanto, que esse remodelamento é qualitativa e quantitativamente diferente do que se observa no câncer de próstata e mesmo em processos de reparo e cicatrização. Nesses casos, por exemplo, estão elevados tanto a expressão do variante “splicing” oncofetal (ED-B) da fibronectina (Albrecht et al., 1999) quanto a atividade da hialuronidase (Lokeshwar et al., 1996), uma das principais enzimas associadas ao “turnover” da matriz extracelular. Na HPB, por outro lado, esses marcadores estão presentes em níveis normais.

Com base em dados prévios (12) e em nossos resultados sobre dermatam sulfato e condroitim sulfato, as proteoglicanas majoritárias do estroma da próstata são decorin/biglican e versican. Este último, um proteoglicano de alto peso molecular e contendo

em torno de 20 cadeias de condroitim sulfato (Iozzo, 1998), estaria aumentado, como indicam nossos resultados, na hiperplasia benigna. Essas conclusões são consistentes com os achados de Walden et al. (6), que, usando como controle a zona de transição, encontraram níveis aumentados de mRNA que codificam proteoglicanos de condroitim/dermatam sulfato no estroma de HPB.

Parte dessas modificações na composição da matriz pode ser explicada por alterações na população de células do estroma, com a substituição, em certas áreas, de células de músculo liso por fibroblastos (9). Adicionalmente, mostrou-se recentemente, na HPB, a presença de grandes quantidades de fator de crescimento de fibroblastos (FGF) básico em células de músculo liso (22), além de um aumento na concentração tissular de isoformas do FGF (Ropiquet et al., 1999). Esta citocina tem potentes efeitos estimulatórios sobre a migração de células mesenquimais (23) e sobre a síntese de proteoglicanos intersticiais (24), o que sugere um mecanismo paracrino nas vias regulatórias que levam ao crescimento e reorganização do estroma na HPB.

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